ANNALS of ALLERGY

Published by
The American College of Allergists

Volume 8 May-June, 1950 Number 3

PYRROLAZOTE, A CLINICAL EVALUATION IN ALLERGIC STATES

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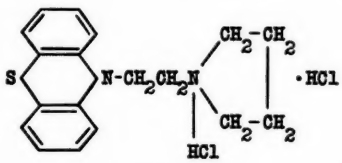
WE are reporting clinical experiences with a new antihistaminic agent, Beta-pyrrolidineethyl-phenothiazine hydrochloride (Pyrrolazote).*



This drug was initially made available in 50 mg. tablets, and the dosage used was varied in accordance with the response of the patient. The usual dose was one tablet twice or three times daily, but larger or smaller amounts were sometimes used.

In Section I of this report there is a record of experiences with these 50 mg. tables of Pyrrolazote in the L.S.U. out-patient clinics of Charity Hospital. In these cases Pyrrolazote was compared with placebo medication (L.C.). In Section II of this study placebos were not employed. An elixir containing 75 mg. per ounce was given to children. The data obtained for this second section were derived from the office records of two of us (H.D.O. and V.J.D.).

SECTION I—METHOD

Forty-six patients with asthma, hay fever, combined asthma and hay fever, and two cases of urticaria were utilized. Patients were selected at random, no attempt being made to differentiate the type of respiratory allergy, i.e., intrinsic or extrinsic asthma, or the type of nasal allergy.

Presented at the Fifth Annual Meeting of the American College of Allergists, April 14-17, 1949, Chicago, Illinois.
*Kindly supplied by the Upjohn Company, Kalamazoo, Michigan.

Patients were alternated from week to week on Pyrrolazote and a placebo for varying periods of fifteen to twenty weeks. Each patient at each clinic visit was given a one-week supply of Pyrrolazote and a mimeographed form to fill out. On this form the patient was to give the time of onset of attacks, severity of symptoms, duration of attacks, the number of tablets taken, and the frequency with which the tablets were taken. These patients were also to record any side reactions that were noted, and to facilitate this a list of symptoms experienced with other antihistaminics was printed on the form. At the return visit the following week, the forms would be evaluated, the Pyrrolazote collected, and a week's supply of placebo issued with a similar form. Patients took Pyrrolazote and placebo on alternate weeks during the study. It should be pointed out that asthma was present in a large percentage of these patients (61 per cent of forty-six). This was due to the fact that there was no selection of patients, and asthmatics are in a large majority in the out-patient allergy service of Charity Hospital. That poor results are obtained with antihistaminics in asthma has long been recognized.

RESULTS

Results were evaluated according to the number of hours of mild, moderate, and severe symptoms while on the drug and on the placebo. Dr. Huldah Bancroft, Professor of Biostatistics, Tulane University School of Medicine, tested the results (Table I).

TABLE I. AVERAGE HOURS OF SYMPTOMS PER WEEK PER PATIENT

	Placebo	Drug	P*
Mild symptoms	4.40 hours	4.33 hours	—
Moderate symptoms	4.09 hours	2.75 hours	0.23
Severe symptoms	10.55 hours	5.08 hours	<0.0001
Moderate and Severe symptoms	14.64 hours	7.83 hours	0.0001
Total symptoms	19.04 hours	12.17 hours	<0.0001

*P = probability that a difference as great as or greater than this would occur by chance. This probability was determined from the formula:

$$C.R. = \frac{\text{Mean}_1 - \text{Mean}_2}{\sqrt{S.E._1^2 + S.E._2^2 - 2r\, S.E._1\, S.E._2}}$$

There was no significant difference between mild and moderate symptoms while on the drug and while on the placebo, but a significant difference in severe symptoms is noted. There were 10.55 hours of severe symptoms per patient per week while on the placebo in comparison with 5.08 hours of severe symptoms per patient per week while on the Pyrrolazote. As great a difference or a greater difference than this would be expected to occur by chance less than 1 time in 10,000. This reduction in the hours of severe symptoms is considered significant. The difference in the total symptoms (mild, moderate, and severe) is also significant. There was an average of 19.04 hours per patient per week while on placebo as compared with 12.17 hours while on Pyrrolazote.

It is felt that the degree of symptoms must be taken into consideration, as it would be faulty to compare hours of severe symptoms with hours of mild symptoms. The severity of symptoms were evaluated by the patients themselves; this, of course, is a subjective evaluation. However, in this study the errors of subjective interpretation were obviously neutralized since both groups were crossed over and because the total hours of all degrees of symptomatology were computed for both groups. Patients were not informed that they were taking placebos.

The results were also evaluated according to statements made by individual patients. These are classified in Table II according to type of case.

TABLE II. RESULTS REPORTED BY PATIENTS

	Pyrrolazote				Placebo			
	Good	Mod.	Poor	None	Good	Mod.	Poor	None
Hay fever and asthma	13	2	2	3	8	2	4	6
Hay fever	13	2	2	0	10	1	3	3
Asthma	3	1	1	2	2	0	2	3
Urticaria	1	1	0	0	0	0	0	2

In the group of combined hay fever and asthma, there was no breakdown in the two syndromes, and some of the five patients with poor or no relief while on the drug might have had relief from nasal symptoms even though the asthma was not benefited.

It is noted that there are a large number of patients who received benefit while on the placebo. However, we feel that in any study of this type this is not unusual. In many of these patients these good results could be attributed to various factors such as excessive co-operation, neurosis, spontaneous disappearance of symptoms which would have subsided without any medication, et cetera. * *

TABLE III. SIDE REACTIONS

	On Pyrrolazote	On Placebo
Mild drowsiness	30	21
Severe drowsiness	1	1
Nausea	13	0
Severe nausea	0	1
Vomiting	6	4
Headache	18	12
Palpitation	1	0
None	8	18

These findings indicate that when patients are warned of possible side reactions and particularly if they have experienced them on the drug, they are quite apt to complain when on the placebo. Possibly certain of the reported side reactions to various antihistaminics are attributable to warnings given to the patient simultaneously with the medication.

**Since this article was submitted for publication, Stewart Wolf in his article, "Effects of Suggestion and Conditioning on the Action of Chemical Agents in Human Subjects," (J. Clin. Invest., 29:100-110, January, 1950) has reported that "placebo effects" which modify the pharmacologic action of drugs or endow inert agents with potency are not imaginary, but may be associated with measurable changes at the end organs. These effects are at times more potent than the pharmacologic action customarily attributed to the agent.

SECTION II

In this part of the study we are evaluating our observations on the drug in 130 patients. Some patients had more than one symptom; therefore the total number of symptoms is larger than the group of patients. In this group the patients were merely given Pyrrolazote tablets and asked to report the results. This is the type of study that has been followed by most clinical investigators with other antihistaminics. We have used it in the conditions listed in Table IV.

TABLE IV

	Good	Moderate	Poor	None
Hay fever	45	6	3	7
Chronic allergic rhinitis	35	2	1	5
Allergic tracheobronchitis	5	0	0	0
Bronchial asthma	6	0	2	5
Urticaria	6	1	0	0
Headache	3	1	0	2
Pruritus ani	3	0	0	0

TABLE V. SIDE REACTIONS

Stimulation	1	Weakness	1
Drowsiness	39	Dizziness	1
Hypnosis	7	Abdominal cramps	1
Nausea	14	None	71

However, since this study was begun, we have commenced using another Pyrrolazote preparation. These are Pyrrolazote-coated delayed action tablets containing 25 mg. of Pyrrolazote base (present as the hydrochloride) in the outer coat, available for immediate absorption. Twenty-five mg. is present in an inner, Ileosol-coated tablet. It is felt that such a tablet will serve to prolong the effectiveness of a single dose of the drug, possibly enough to carry through the sleeping hours of the patient. It had previously been observed that many patients would do well on half of the 50 mg. tablet and that the incidence of side reactions was thereby greatly reduced.

TABLE VI. PYRROLAZOTE—TWO STAGE (32 PATIENTS)

	Good	Mod.	Poor	None
Hay fever	3	1	0	1
Chronic allergic rhinitis	11	3	0	1
Urticaria	3	1	0	0
Bronchial asthma	1	0	0	0
Allergic tracheobronchitis	1	0	0	0
Headache	1	0	0	0
Rhinitis medicamentosa	0	0	0	1
Atopic eczema (relief of itching)	1	0	1	0
Pruritus	3	0	0	0
Localized neurodermatitis	0	0	0	1

Two of these patients had more than one symptom. Slight drowsiness appeared in two of them, and some nausea in three.

In addition to the two groups reported above, Pyrrolazote tablets (usually the two-stage type) were later used in an additional twenty-six office patients (H.O.). Six patients had more than one symptom. The results reported were as follows:

TABLE VII. PYRROLAZOTE—MIXED OFFICE GROUP

	Good	Moderate	None
Urticaria	5	0	1
Chronic allergic rhinitis	13	2	3
Asthma	1	0	1
Contact dermatitis	1	0	0
Conjunctivitis	0	0	2
Hay fever	2	0	0
Vomiting	1	0	0

Three patients reported slight drowsiness and one had marked drowsiness. One patient complained of insomnia, while another had dizziness and headache. It is felt that the percentage of side reactions is greatly lessened when the two-stage preparation is used. No attempt is made in the paper to combine these three groups, because the plain and two-stage tablets have a different period of action.

In scratch tests sites of three patients that were treated with 5 per cent Pyrrolazote solution (sterile), definite inhibition of histamine flares were observed. In another patient inhibition of a ragweed skin reaction was obtained.

CONCLUSIONS

1. Pyrrolazote is a potent antihistaminic which compares favorably with other similar preparations.
2. Placebo controls show that there is a significant difference in amount of severe and total symptoms while on the drug.
3. A large percentage of patients taking placebo tablets complained of side reactions. Therefore, the element of suggestion must be considered in evaluating such reactions to any antihistaminic.
4. The new two-stage tablet appears to be effective. Side reactions were mild and infrequent.

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CORRECTION

In the January-February issue of ANNALS OF ALLERGY, "Allergic Toxemia and Fatigue" by Albert H. Rowe, M.D., F.A.C.A., there appeared two references to Tomas Mariante. The first is on page 72, line 12; the second on page 79, reference 2. The author of the work cited, *Toxemia Alergica*, is Nino Marsiaj, M.D., F.A.C.A., Brazil. Dr. Mariante was also a contributor to the book, but the article on allergic toxemia was written by Dr. Marsiaj.

SOME ASPECTS OF ALLERGY OF THE EYE

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THE history of this subject is well known. The monograph "Die Anaphylaxie in der Augenheilkinde" of von Szily, [17] published in Stuttgart in 1914, coupled with that excellent one nearly twenty years later by Professor A. C. Woods,[20] provides an historical background for the present paper.

The first important study of allergic conditions of the eye in England was published by Blackley[2] of Manchester: "Experimental Researches on the Cause and Nature of Catarrhus aestivus." It is not generally known that Blackley published a second edition in 1880, adding two more chapters devoted to treatment. Blackley's graphic description of the conjunctival test with locally grown pollens is well worth recalling:

Para. 136. "A decoction of the pollen of Gladiolus was made by boiling a portion of this with one hundred times its weight of distilled water. One drop of this liquid was placed in contact with the conjunctiva of the right eye. The effect was almost instantaneous. The first sensation was that of intense burning and smarting, coupled with a feeling such as might be imagined to be caused by fine sand being blown into the eye. The photophobia was so severe that for some minutes the eye could not be opened for more than a single second at a time. In about thirty seconds the capillary vessels of the conjunctiva were seen to be greatly distended. With the aid of a lens the larger vessels of the conjunctiva could be seen to be raised above the surface. Movement of the eyeball gave great pain, just as is felt when dust has been blown into the eye. In six minutes the conjunctiva had become quite edematous, but showed its closer attachment as far as the outer margin of the cornea. The edema increased until very severe chemosis was set up. The eyelids also became much swollen. In two hours after the fluid had been applied the smarting and burning had much abated, and the congestion of the conjunctival vessels had considerably lessened, but the chemosis remained and was even more marked than it had been an hour before. There was a moderately copious discharge of fluid from the eye and also some little from the nostril. In six hours the eye still felt uneasy, but there was very little pain on moving the eyeball, although the vessels of the conjunctiva were still injected. The chemosis still remained as severe as before. In eighteen hours there was scarcely any congestion of the vessels remaining, but the chemosis was still very distinct. In thirty-two hours all traces of the derangement had disappeared. During the course of this experiment no effect was produced on the sclerotic coat of the eyeball, nor yet, so far as could be seen or felt, on the deeper structures. The action seemed to expend itself upon the conjunctiva and upon the cellular tissue of the eyelids."

A generation later this conjunctival test was extended and used by Noon and Freeman.[4] Noon[10] was a great observer. He used as little as five to seven grains of pollen for "active immunity" treatment, and knew that if he used larger doses, he did harm rather than good. In recent times this has been replaced by other tests, less embarrassing, and perhaps less dangerous for the patient.

Presented at the Sixth Annual Meeting of the American College of Allergists, St. Louis, Missouri, January 17, 1950.

This study is based on 17,150 cases observed over a period of ten years.

TABLE I. EYE HOSPITAL OUTPATIENTS

Presenting Pathologic Condition	Approximate per cent of Cases Proved to be of Allergic Origin 1941-6	1941-9
Angioneurotic edema	70	70
Blepharitis	10+	15
Conjunctivitis	40+	43
Keratitis	10	10
Keratitis rosacea	70	78
Episcleritis	7.5	8
Iritis	3	8
Iridocyclitis	2.5	11
Glaucoma	5	5
Acute congestive glaucoma	—	15
Retinal hemorrhage or detach	1	1
Choroiditis	3	3
Cataract	0.2	0.4
Retro-bulbar neuritis	—	45
Migraine	54	63

In opening a discussion on "Allergy in Ophthalmology" at the Royal Society of Medicine in 1947, Mr. Gayer Morgan[5] (senior ophthalmic surgeon at Guy's Hospital) reminded us that almost every disease of the eye had been reported as allergic in origin in some particular case. The truth of this statement is all too obvious from the copious literature on the subject, but how much more widely applicable if we delete the word "disease" and replace it by "condition." To me an allergic condition is acute in onset, and if recognized and treated at once will clear up quickly, often within a few minutes or hours, leaving no permanent damage to the tissues involved; but it must be recognized that once a tissue has remained in an abnormal physiological condition for some time, as in recurrent keratitis or iridocyclitis, there may be secondary changes due perhaps to pressure of edema, to inflammation, or to secondary infection, which must be healed by routine treatment and may leave permanent scarring.

To explain why one organ, be it eye, ear, chest or skin, is selected as the "shock tissue" to carry the full responsibility of an allergic reaction, takes us into the realm of metaphysics: and indeed I hope to demonstrate that not the eye as a whole but one tissue only (perhaps conjunctiva, cornea, iris, lens, et cetera) is, as a rule, concerned in the manifestation of allergy in any given patient. Why any one tissue is selected for such abuse we do not know. Many readers may believe, and perhaps rightly, that some previous injury, either traumatic or developmental, is necessary. This idea seems to help in the explanation of unilateral allergic conditions in one of two symmetrical organs.

Depending on which tissue is sensitized to the offending allergen, we may see angioneurotic edema, blepharitis, conjunctivitis, keratitis, episcleritis, iritis, iridocyclitis, glaucoma, retinal hemorrhage or detachment, chorioditis, cataract, retro-bulbar neuritis, or migraine.

From Table I it can be seen that some of these conditions are frequently allergic and some only occasionally so. The first column of figures (1941-6) was published in the *British Journal of Ophthalmology* in 1948 (Walker[18]). Three more years' investigations have been added, and the results summarized in the second column are complete up to 1949. Several points deserve comment:

Angioneurotic Edema.—An allergic cause can be found for 70 per cent of these edemas, but if we included only those patients who, during the attack, have some other associated manifestations of allergy such as conjunctivitis, edema of cornea, or migraine, this figure increases considerably, and practically 100 per cent are proved to be allergic in origin. Presumably those of psychosomatic and hormonal origin would thus be eliminated from the series.

Acute Iritis.—Acute iritis, with or without involvement of the ciliary body, is occasionally presented to the allergist for investigation, especially when the patient is a chronic asthmatic. The psychological trauma due to sudden acute pain may precipitate an attack of asthma, and so help in the diagnosis. When one remembers that the iris is a "diaphragm of blood vessels and unstriped muscle fibres held together by a very loose spongy stroma" (Parsons and Duke-Elder,[11]) one cannot fail to recognize an almost ideal setting for an acute anaphylactoid reaction. While the routine treatment of atropine and heat must be applied in all acute iritis cases, if the attack is possibly of allergic origin 1 c.c. of epinephrine 1/1,000 injected subcutaneously, slowly, will relieve the pain in a few minutes instead of in hours or days. Such acute iritis cases may be due to foods, inhalants, drugs or toxins (including tuberculin), and should have the advantage of a full range of allergy tests between, not during, acute attacks.

Iridocyclitis.—The increase from 2.5 to 11 per cent (Table I) is partly explained by inclusion of some post-accident cases of acute cyclitis. The trauma of the accident may act as a trigger for some allergic response to airborne allergens or drugs; or if the lens capsule is torn in any accident, the surrounding tissues become sensitized by the escaping material. The stage is now set for an allergic response in this, and perhaps also in the other eye, if any operative procedure is necessary during the next few days or weeks. A typical example is described in Case 1.

Case 1

Male, aged 38

1st day..... Perforating injury of left eye with lens puncture. No F.B. found. Routine treatment in hospital, including penicillin locally.
10th day..... Reported at Outpatients. No pain but worried by loss of vision. Curette evacuation of swollen lens (not whole) and A.C. washout.
11th day..... Acute cyclitis of L. eye and some discomfort in R.
12th day..... Severe cyclitis in L. eye. Slight iridocyclitis in R. (Sympathetic ophthalmitis).
12th day a.m. ..... Routine allergy tests. All inhalants, pollens, foods and drugs negative.
12th day p.m. Uveal pigment —ve
Lens protein +++ (intradermal)
Desensitization to lens protein by graded intramuscular injections 3-hourly for 3 days.
15th day..... R.E. normal in appearance and vision.
L.E. still slightly injected but all discomfort gone. Vision 20/120.
17th day..... Further washout of A.C.
Lens protein disturbed without any flare-up.
23rd day..... Vision R.E. 20/20 Discharged from hospital.
L.E. 20/80
53rd day..... Vision R.E. 20/20
L.E. 20/80

Also included in the 1949 list, but not in the 1946 one, are those cases of chronic recurrent iridocyclitis of which it had been agreed by the ophthalmologists and pathologists that the inflammation was of "virus origin."

TABLE II. ACUTE CONGESTIVE GLAUCOMA

Case	Allergen Found	Treatment		Time Before Tension Normal
		General	Local	
Male (44)	Pollen	Epinephrine Adrenaline 1 c.c.	Eserine	6 hours
Female (56)	Pollen	Epinephrine Adrenaline 2 c.c.	Pilocarpine	3 hours
Female (62)	*Streptococcal protein	Anthisan	Pilocarpine	20 hours
Female (65)	Tomatoes	Benadryl	nil	4 hours
Male (56)	†Fish, Uveal pigment	Benadryl	Eserine	16 hours

*Complicated by bronchiectasis.
†Known to have "fish" asthma all his life.

So far, although we have frequently used bacterial allergens prepared from streptococcal, staphylococcal or tubercle protein, no attempt has been made in our hospital to prepare a virus allergen. Some persons will champion the view that recurrent clinical manifestations of virus disease, occurring after an incubation period, are due to propagation of the virus itself, rather than to a development of hypersensitivity, and so to attainment of a state of clinical allergy. All viruses are not self-limiting, so in the absence of any satisfactory drug treatment for the viruses themselves we find that a state of stagnant depression of both doctor and patient rapidly develops, becoming more intense with each recurrence, as the threat of ultimate blindness looms on the horizon. In an attempt to help in what is perhaps a losing fight, treatment of chronic iridocyclitis by nonspecific antiallergic methods is being explored. Results are not yet ready for publication, but a pilot survey indicates that the use of full doses of antihistaminics by mouth during an acute exacerbation, followed immediately by desensitization with histamine, overcomes the tendency to recurrences, and so delays any deterioration of vision, perhaps for years. The tentative suggestion is made that the tendency to develop a state of clinical allergy has been reversed. So in Table I the figure of 11 per cent includes not those iridocyclitis cases, reporting once and once only, caused by acute infection or trauma, but those who have come with a first or subsequent recurrence, and after receiving what may be loosely termed "reduction of sensitivity" treatment, have avoided further recurrence for at least three years.

Acute Congestive Glaucoma.—It is often recorded in hospital notes that the pain of acute glaucoma was intense enough to cause vomiting; further questioning of the patient will sometimes elicit the statement that the biliousness started *before* the pain, and indeed that there had been previous attacks of vomiting accompanied by some transient dimness of vision with or without neuralgia in the region of the fifth nerve. This, together with the edema of lids and conjunctiva and the venous dilatation causing dusky red coloration of conjunctivae, the cloudiness and lack of sensitivity to

TABLE III. KERATITIS ROSACEA I

100 Patients (1940-1947)

	Presenting Symptom	
Group I	Face lesions only	23
Group II	Face lesions + palpebral conjunctivitis	18
Group III	Face lesions + palpebral and bulbar conjunctivitis	28
Group IV	Face lesions + conjunctivitis and slight keratitis	10
Group V	Face lesions + keratitis with severe scarring	21
		100

All of these, if untreated, are potentially in Group V.

TABLE IV. KERATITIS ROSACEA II

Group A. (Table III) Allergic cause for both face and corneal lesion found by skin tests, exclusion diets, contact history etc.	78
Group B. No proof of allergic origin of lesion	22
	100

touch of the cornea, and the discoloured iris, suggests an acute allergic state, and may be proved to be so in at least 15 per cent of cases. Typical examples are shown in Table II.

The work of Kirwan[8] should be recalled. He investigated the glaucoma associated with epidemic dropsy in India and reported that the essential feature is a capillary dilatation and increased permeability throughout the uveal tract due to the action of a histamine-like substance present in the aqueous and vitreous, which is also responsible for the general tissue edema in this epidemic dropsy. Though the tension was often raised to near 100 mm. Hg (Schiötz), local treatment was valueless, but the eye condition began to improve when general treatment was instigated. This consisted of eliminating rice from the diet and washing out the alimentary tract. Allergists will appreciate the probability that not the rice, but rather some mold on the rice may have been the responsible toxin.

[Pathology: Ciliary body showed vascular dilatation and edema of tissues without abnormality of the epithelium. Enormous vasodilatation in the choroid. Filtration angle shows complete absence of abnormality.]

Keratitis.—Although only 10 per cent of all cases of keratitis seem to come into the allergic group, a very much greater figure is obtained in a sub-group with those where the corneal lesion is associated with rosacea. Rosacea is the presenting symptom of an abnormality of the superficial epithelium of the face of adults between the ages of twenty and fifty years. An attack may last a few weeks or months, but tends to clear up only to recur again at increasingly frequent intervals, eventually being accompanied by ocular manifestations, varying in degree from a mild conjunctivitis through all the stages of blepharo-, tarsal- and bulbar-conjunctivitis to keratitis, and eventual visual incapacity.

[Pathology of skin lesions of rosacea (Roxburgh):[14] Dilatation and

TABLE V. KERATITIS ROSACEA III

Group A = Specific Allergy Found

Treatment	Number	No Further Attacks in:		
		6 months	2 years	5 years
Desensitized by injection	42	36	34	34
Desensitized by mouth to food	8	4	4	4
Avoided allergens	28	25	20	18
	78	65 83%	58 74%	56 72%

TABLE VI. KERATITIS ROSACEA IV

Group B = Specific Allergy Not Found

DESENSITIZATION WITH HISTAMINE			
Total No.	No Further Attacks In:		
	6 months	2 years	5 years
22	15 70%	10 45%	9 41%

new formation of capillaries in upper third of the corium. Infiltration with small round cells and later with epitheloid cells and giant cells. This infiltration occasionally forms semi-translucent brown nodules of lupus vulgaris. Degeneration of elastic tissue in the papillary layer. Hypertrophy of the sebaceous glands. Later the nodules of infiltration break down into pus and many collections of polymorphs are then found in the corium in all stages of degeneration. Scarring follows the healing of these abscesses.]

In Group II one probably sees only scaly desequamation of the lids without permanent scarring; then in Group III there is engorgement of the vessels of both tarsal and bulbar conjunctiva accompanied by considerable irritation and some photophobia; the lacrimal flow is scanty and watery. If it becomes muco-purulent a secondary infection should be suspected, as the white ropy discharge of hay-fever with its 70 per cent eosinophilia is not seen in uncomplicated rosacea. Occasionally grey nodules resembling those seen in phlyctenular-kerato-conjunctivitis appear on the bulbar conjunctiva. These nodules are surrounded by a typical network of varicosed vessels, and histologically are follicles of lymphocytes with epitheloid cells in the center. Similar nodules may sometimes be seen on the episclera.

The first sign that the cornea is involved (Group IV) is marginal vascular infiltration, which was described as a valuable diagnostic feature by Triehenstein.[16] This infiltration is followed by development of subepithelial deposits and the assemblage of permanent scar tissue (Group V). For typical appearance of such lesions see Mr. Doggart's book, "Ocular Signs in Slit-lamp Microscopy" (London, 1949).

Numerous as the list of possible causes of keratitis rosacea may be, almost all authors agree that the condition is a "systemic rather than a

local one." Digestive upsets, deficiency diseases and hormonal disorders all play a part, and must be treated appropriately, but even after all these have been corrected and the attack of the moment healed, there is still an underlying condition which predisposes to recurrence. As early as 1864 Arlt[1] recognized that ocular treatment was useless unless combined with treatment of the associated lesions of the face. A survey of investigation and treatment during the last ten years shows that allergy plays a fundamental part in the syndrome.

It cannot be emphasized too often or too strongly that every case of true rosacea is a potential candidate for the "blind" list. If possible before marginal vascular infiltration shows that the cornea is involved, a warning should be given.

From the preceding tables and the following case-sheets it becomes clear that if recurrences can be prevented, the vision will not deteriorate further; that is, *the condition will be arrested.* Case 2 is an example of those who, having had no treatment for the allergic condition, proceed to ultimate blindness; whereas in such cases as 3, 4 and 5, vision was arrested.

Case 2

Male, aged 45

Lesion	*Vision* R.E.	L.E.
1930 lesions of face	20/20	20/20
1935 lesions of face + keratitis	20/30	20/60
1940 keratitis	20/120	20/60
1945 lesions of face + keratitis	20/120	20/200
1949 lesions of face + keratitis	20/200	nil

No investigation or treatment in Allergy Department at any time.

Case 3

Male, aged 52

Lesion	*Vision* R.E.	L.E.
1932 lesions of face	20/20	20/20
1935 lesions of face + conjunctivitis	20/20	20/20
1939 lesions of face + conjunctivitis + corneal ulcer	20/30	20/20
1942 lesions of face + keratitis	20/60	20/60
1946 severe keratitis referred to Allergy Department**	20/200	20/120
1949 face and eyes quiet but cornea scarred	20/120	20/120

**Was desensitized in 1946 to feathers, cat-fur and house-dust.

DISCUSSION

Attention is drawn to the common denominator of all the cases reported above: underlying all of them, whether conjunctivitis, keratitis, iritis or glaucoma, is that elusive "allergic state," recently described by Williams[19] as a "clinical phenomenon." Each physician's conception of this is perhaps as personal and varied as that of each individual patient.

Case 4

Female, aged 64

Lesion	*Vision* R.E.	L.E.
1935 lesions of face	20/20	20/20
1941 lesions of face + conjunctivitis	20/20	20/40
1946 lesions of face + conjunctivitis + keratitis	20/60	20/40
1947 lesions of face + keratitis referred to Allergy Department**	20/80	20/120
1950 face and eyes quiet but cornea scarred	20/80	20/80

**Desensitized by injection with allergens of orris root, feathers and house-dust in October, 1947.

Case 5

Female, aged 43

Lesion	*Vision* R.E.	L.E.
1930 lesions of face	20/20	20/20
1933 lesions of face + conjunctivitis	20/20	20/20
1939 lesions of face + keratitis	20/30	20/60
1940 keratitis referred to Allergy Department**	20/60	20/120
1942 lesions of face + keratitis	20/30	20/120
1949 face and eyes quiet	20/30	20/120

**Complicated by myxedema. Has required thyroid therapy daily since 1939. Been desensitized with histamine three times in nine years.

Rosenow and Nickel[13] published from the Mayo Clinic in 1932 some brilliant work on elective localization in determining the etiology of chronic iridocyclitis. They emphasized the development of hypersensitivity of the tissues due to remote foci of infection, e.g., of tonsils, teeth, prostate, or cervix. An important modern extension of this work comes from Stokes and Beerman[15] of Philadelphia, and published this year in *Archives of Dermatology and Syphilology*. These authors write of a virus-pyogen sensitization sequence and make valuable suggestions for researches as soon as the appropriate viruses have been isolated, though they are fully aware of the importance of other elements of a complex background including other allergens, emotional stress, or exhaustion.

Whether we are faced with a typical phlyctenular conjunctivitis, a nodule of keratitis rosacea, or a reversible or indeed an irreversible dilatation of the vessels of the iris, one possibly common explanation exists, i.e., an allergic response to an *endogenous* toxin or allergen occurring typically in a patient with some metabolic instability. Perhaps it is not generally realized that *exogenous* dusts or pollens may be responsible for any or all of these manifestations, as often as bacterial proteins or food decomposition products.

From the work of Gutmann[6,7] on conjunctivitis and spring catarrh (in which riboflavin appeared to enhance the action of adrenaline on small superficial vessels of the eye) and of Miles Atkinson[9] on Ménierè's disease (in which he described two types of vertigo—rotational, helped by nicotinic acid, and positional, helped by riboflavine) it looks as if riboflavine is

one of the substances capable of masking or neutralizing a metabolic weakness in epithelial cells favored by the strain of the allergic state (Pollak).[12]

Seventeen years ago A. L. Brown[3] of Cincinnati, while working on considerations underlying experimental production of uveitis, suggested that the *recurrences* of iritis might represent "periods of hypersensitivity" and the *remissions* "periods of desensitization." The possibility of self-desensitization by human organisms might help to explain the periodicity of some allergic conditions, but until we have directed the full weight of our attention to understanding and possibly finding some way of compensating this allergic state of our patients, we are a very long way from being masters of our science.

ACKNOWLEDGMENT

I should like to record my appreciation of the generosity of the American College of Allergists in making possible my visit to the St. Louis conference; also to thank all those ophthalmologists who have allowed me to investigate and treat their patients. I am especially grateful to Mr. Humphrey Neame, Mr. Gayer Morgan, and Mr. Doggart, all of London, for permission to use drawings of their cases to demonstrate the appearance of typical allergic lesions of the cornea, and to Mr. Theodore Hamblin for his kind and courteous help throughout.

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AEROSOLS III. AN INSPIRATION-TIME METER FOR QUANTITATIVE MEASUREMENT OF THE INHALATION PERIOD OF MISTS

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IN a preceding communication[1] it has been shown with standard phenolsulfonphthalein aerosols that, using procedures of nebulization now in use, there are many variables involved in measuring the quantity of aerosol deposited in and absorbed from the lungs. It seemed desirable because of the extensive interest in therapeutic, toxic, and antigenic aerosols, to ascertain whether the reproducibility of the renal excretion of inhaled phenolsulfonphthalein mists was primarily dependent upon the time of and character of inspiration, other conditions being essentially constant. A stop watch was found to be unsuitable for measuring the exact time of inspiration. Some mechanical means of automatically recording the inspiration time was evidently required. An inspiration-time meter, for use with aerosols in general, is now described. Its application to the production of experimental asthma under more controlled conditions is demonstrated. With available data it will be shown, using comparatively simple equipment, (1) what the nature of the respiratory cycle during certain kinds of aerosol therapy is, and (2) how the time of inspiration of the aerosol administration can be more quantitatively measured. In this way, improvement in the technique of inhalation of aerosols is obtained by standardized and predictable procedures.

METHOD

In earlier unpublished experiments designed to follow the nature of the respiratory cycle during aerosol therapy, attempts were made to design equipment which would be activated directly by the patient's respiration, e.g., a thermocouple in the nebulizer-patient path. All of these attempts were unsatisfactory because of the difficulties of using the patient himself as the activating device. In the technique here described, the back pressure which is set up when the aerosol is generated by placing a finger over the cut-off valve (Figs. 1 and 2) is used to force a mercury column to establish a contact in the electric circuit maker, *A*. The circuit maker, *A*, establishes a current in the interval-timer, *B*, which flashes a light and acts as a supplementary timing device to the electric stop watch, *C*, equipped with an automatic brake. This stop watch can easily be read to a tenth of a second. The total period of inspiration as well as each individual inspira-

Presented at the Sixth Annual Meeting of The American College of Allergists, January 15-18, 1950, St. Louis, Missouri.

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This investigation was supported in part by a research grant from the Division of Research Grants and Fellowships of the National Institute of Health, United States Public Health Service and the Foundation for Research in Pulmonary Disease, New York, N. Y.

The authors are indebted to Hynson, Westcott and Dunning, Baltimore, Maryland, for supplies of phenolsulfonphthalein.

tion is readily read on the dial of the stop watch and recorded. The stop watch is connected to a special outlet in the interval-timer, *B*. In addition to the stop watch there is also an electric counter, *D*, which simultaneously records the number of inspirations. This equipment is designed for re-

Fig. 1. Proper position of the nebulizer and components of the Inspiration-Time Meter. The back pressure in the circuit forces a mercury column in the U-tube, *A*, to establish a current in the Interval Timer, *B*. The electric stop watch, *C*, is equipped with an automatic brake. A counter, *D*, gives the number of inspirations. This arrangement is convenient for research purposes. For routine therapy neither the Interval-Timer, *B*, nor the counter, *D*, is required. The circuit maker, *A*, may be attached directly to the electric stop watch, *C*.

search purposes; for therapeutic purposes, neither the interval-timer, *B*, nor the electric counter, *D*, is required. All that are necessary for routine therapy are the circuit-maker and the stop watch *C*. For example, in quantitative therapeutic procedures, the nurse may merely be told to administer for 50 seconds a solution of glycerite of epinephrine 1:100, or 500 seconds of penicillin aerosol at a given volume-velocity of oxygen. In this way the actual time which the patient inspires the material may be simply recorded. The total time of experiment is measured by a manually controlled stop watch.

It is evident that the inspiration-time meter, as illustrated in Figures 1 and 2, can also be used (1) to control the amount of aerosol administered in producing experimental asthma with histamine, acetylcholine compounds and allergens like ragweed solutions, and (2) with the therapeutic agent to estimate the quantity of inspired aerosol administered to control the

asthma. By using an inspiration-time meter of this type, many of the contradictory statements found in the current aerosol literature, based upon experiments consisting of a small number of squeezes of a nebulizer bulb to deliver the agent studied, may be clarified.

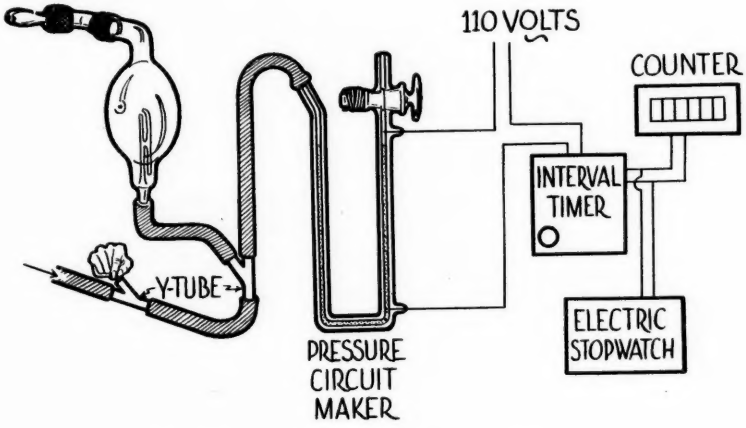

Fig. 2. This diagrammatically illustrates the Inspiration-Time Meter shown in Figure 1. As the finger occludes the *Y* tube, gas is forced through the atomizing unit in the nebulizer. This establishes a back pressure which forcibly thrusts the mercury column upward against the pressure stop cock. This establishes the electric circuit, thus simultaneously activating the Interval-Timer (30 minutes total time), the electric stop watch and the counter.

TABLE I

All experiments in this group were performed on a male subject, B. S. Vital capacity 4.8 liters. Weight 187 pounds; height 5 feet 11 inches. Inspiration time was measured with the Inspiration-Time Meter. Phenolsulfonphthalein solution contained 68 mg. per c.c. Sufficient solution (1 to 5 c.c.) was initially placed in the nebulizer dependent on the inspiration time of experiment. Volume velocities of oxygen are flowmeter readings (uncorrected) at the tank between 8 and 9 liters per minute.

1 Expt. No.	2 Date	3 Total Time Sec.	4 Inspiration Time Sec.	5 Average Inspiration Time Sec.	6 Number Inspirations	7 Dye Excreted in 2 hrs. mg.	8 Ratio: Insp. Time Total Time
IT-1	4/19	300	183	5.9	31	0.88	0.61
IT-2	4/20	600	348	4.8	73	3.55	0.58
IT-5	4/27	300	205	7.1	29	1.70	0.68
IT-6	4/28	600	363	5.3	68	3.50	0.60
IT-7	4/29	900	553	5.2	106	7.0	0.61
IT-10	5/25	490	300	7.6	39	2.66	0.61
IT-12	5/30	840	500	6.1	82	10.20	0.59
IT-17	6/17	160	100	7.1	14	0.60	0.62

EXPERIMENTAL

Using the inspiration-time meter, experiments on the urinary excretion of 5 per cent phenolsulfonphthalein solution inhaled as an aerosol was studied on B.S. from 100 seconds to 553 seconds. The data of these experiments are given in Table I. The average inspiration time is prolonged so that the ratio of the inspiration time to the total time is close to 0.6 or more. The dye excreted in two hours varied from 0.6 mg to 10.2 mg.

Since the method has an inherent error of 0.2 to 0.4 mg due to the pigments in the urine, the lower values are only approximate. To establish relationship between inspiration time and dye excreted in two hours, the data obtained on this one subject, B. S., from Table I, are plotted in Figure 3, up

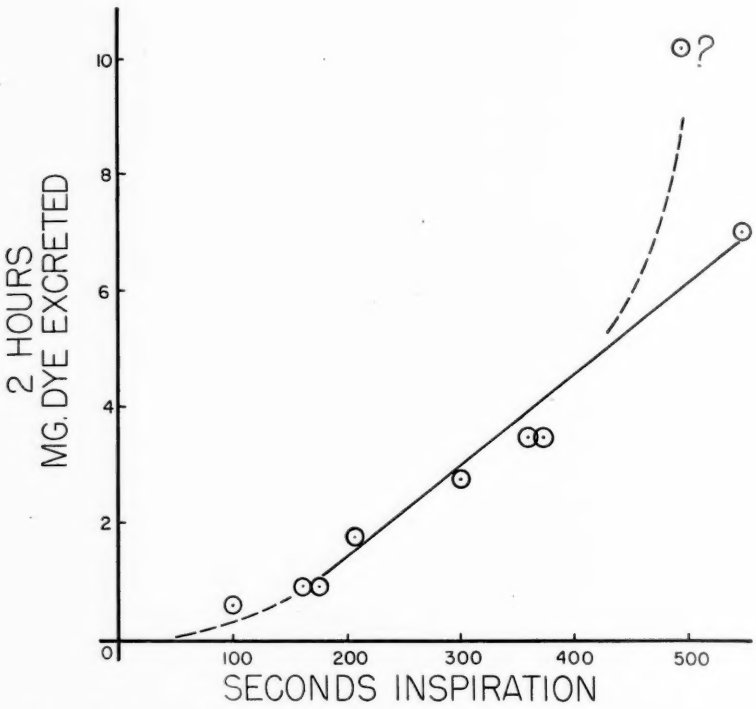

Fig. 3. The data obtained on one subject, B. S., from Table I are plotted in this figure, up to 553 seconds of inspiration time. Seven random experiments fall on a straight line. If the linear relationship extrapolated to zero dye excretion, there would be a threshold of excretion at 120 seconds. However, this is not true because at 100 seconds an appreciable amount of dye appears in the urine. The excretion of the dye, therefore, rises fairly slowly with inspiration time up to about 170 seconds, a linear relationship then appearing for the next 300 seconds. The point off the curve with the question mark at about 500 seconds cannot be explained at present.

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A typical experiment performed on B. S. with the dye is illustrated in Table II. The general outline of Table II may be used to plan experiments

TABLE II. TYPICAL INSPIRATION-TIME METER EXPERIMENT ON LUNG CLEARANCE

A. SUBJECT: B. S.

Expt. No. IT-15, 6/10, started at 10:30 A.M.

A DeVilbiss No. 40 nebulizer was used with nasal tips and L-tube with the vent closed. The initial volume of phenolsulfonphthalein was 3 c.c., each c.c. containing 47.0 mg. (total dye—141 mg). A volume velocity of 8 liters per minute was used.

A benzedrine inhaler was used to shrink the nasal mucosa. The bladder was emptied followed by drinking 500 c.c. water.

B. INSPIRATION CHARACTERISTICS

Total number of inspirations..... 69
Average inspiration..... 7.2 seconds
Total inspiration time.....500 "
Total experiment time.....780 "

$$\text{Ratio: } \frac{\text{Inspiration Time}}{\text{Total Time}} = \frac{IT}{TT} = 0.62$$

C. DELIVERY

Nebulizer residue	55	mg.
Deposit in L-tube	11	mg.
Deposit in nasal tips	11.4	mg.
Total residue	77.4	mg.
Delivered to subject:	63.6	mg.

D. EXCRETION OF DYE IN THE URINE

Specimen	Time	Vol. of Urine	Mg. Dyes
1st	½ hour	25 c.c.	0.97
2nd	1 hour	30 c.c.	2.40
3rd	2 hours	45 c.c.	2.48
4th	3 hours	50 c.c.	1.52
5th	4 hours	80 c.c.	0.93
6th	5 hours	60 c.c.	0.27
		Total dye excreted:	8.57

E. INDIVIDUAL INSPIRATIONS

Column 1 is the inspiration number. Column 2 is the reading on the stop watch. Column 3 gives the duration of inspiration in seconds.

1.	*2.*	*3.*	*1.*	*2.*	*3.*	*1.*	*2.*	*3.*
1.	12.1	**12.1**	24.	178.5	8.7	47.	362.8	7.0
2.	23.1	**11.1**	25.	189.1	10.6	48.	370.6	7.8
3.	31.3	**8.2**	26.	197.8	8.7	49.	378.9	8.3
4.	38.4	**7.1**	27.	204.8	7.0	50.	385.3	6.4
5.	45.3	**6.9**	28.	212.2	7.4	51.	393.0	7.7
6.	54.1	**8.8**	29.	220.0	7.8	52.	399.5	6.5
7.	61.2	**7.1**	30.	228.0	8.0	53.	404.7	5.2
8.	65.7	**4.5**	31.	236.7	8.7	54.	410.5	5.8
9.	73.1	**7.4**	32.	245.9	9.2	55.	416.0	5.5
10.	81.1	**8.0**	33.	253.1	7.2	56.	421.8	5.8
11.	87.8	**6.7**	34.	261.5	8.4	57.	427.0	5.2
12.	93.7	**5.9**	35.	268.8	7.3	58.	433.0	6.0
13.	99.8	**6.1**	36.	276.5	7.7	59.	437.2	4.2
14.	106.5	**6.7**	37.	284.3	7.8	60.	443.6	6.4
15.	113.4	**6.9**	38.	291.9	7.6	61.	448.0	4.6
16.	119.9	**6.5**	39.	301.2	9.3	62.	453.2	5.2
17.	126.7	**6.8**	40.	309.1	7.9	63.	459.3	6.1
18.	134.0	**7.3**	41.	317.6	8.5	64.	467.4	8.1
19.	141.3	**7.3**	42.	325.6	8.0	65.	474.5	7.1
20.	148.3	**7.0**	43.	333.4	7.8	66.	482.1	7.6
21.	156.1	**7.8**	44.	341.1	7.7	67.	488.9	6.8
22.	163.0	**6.9**	45.	348.3	7.2	68.	495.4	6.5
23.	169.8	**6.8**	46.	355.8	7.5	69.	500.2	4.8

on the delivery of aerosols and need not be restricted to dyes. A similar form can be used with histamine, mecholyl, allergens, or penicillin aerosols as well as sympathomimetic amines. Note in Table II the following points: the volume of 8 liters of oxygen per minute (Section A) is uncorrected and might be slightly higher (about 10 per cent). In comparing therapeutic aerosols similar to sympathomimetic amines, this value should be more

precisely obtained. The total number of inspirations in the experiment in Table II was sixty-nine (Section B) with the average inspiration time, 7.2 seconds. It is of interest that, in general, the total inspiration time (Table I) shows that with this technic the ratio of inspiration time to total

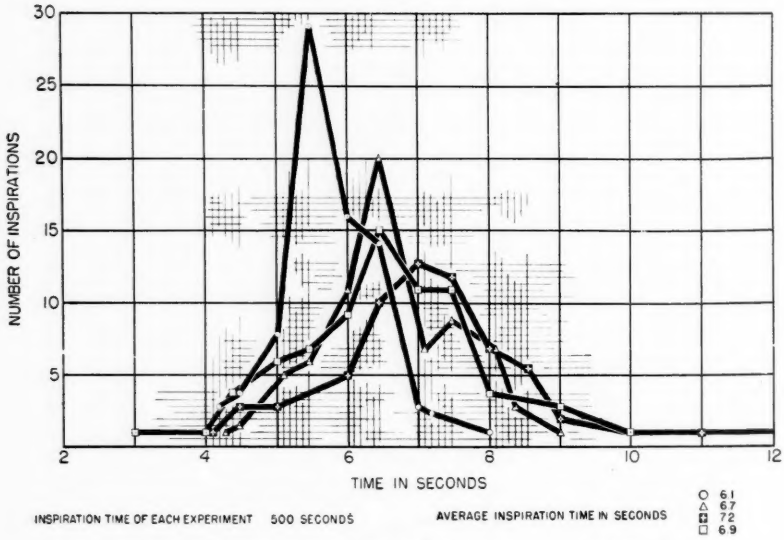

Fig. 4. Population distribution curves of the inspiration times on one subject, B. S.

time is prolonged, thus automatically increasing the probability of deposition in the lungs. Forty-five per cent of the dye originally contained in the nebulizer (Section C) was delivered to the subject. Some of the dye, as mentioned hitherto, is deposited in the nose. Nevertheless, at least 8.57 mg of the dye were excreted in the urine in five hours. This amounts to 13 per cent of that delivered to the subject. In other experiments this value has been higher. Since a certain amount of the dye is lost following intravenous administration (approximately 30 per cent), and since the inhalation of aerosols is somewhat similar to intravenous administration of the dye, we may conclude from this experiment that at least 15 per cent of the dye delivered to the subject passed through the lungs. This value, although low, is definite and shows that antibiotics and other drugs used in aerosol therapy may be subjected to precise independent study by this technic. Section E, Table II, lists in detail the number of inspirations, the reading, and the duration of single inspirations. In general, this experiment is typical of the variations found on inspiration.

Distribution of Inspirations on Subject B. S.—Section E in Table II illustrates how the time of individual inspirations can be accurately recorded during the inspiration of aerosols. Four experiments on B. S.

with a total inspiration time of 500 seconds were studied in this way. The inspirations were then grouped according to inspiration times given in Figure 4 and plotted against the number of inspirations to obtain the distribution curves of the inspiration times of B. S. The inspiration times of this subject vary from about six to seven seconds, as illustrated in the Figure, and give somewhat skewed distribution curves, the significance of which on this subject is unknown. Shorter average inspiration times were observed, e.g., as low as two seconds in anxiety states. The distribution curves, therefore, as shown in Figure 4, may also be connected with the mental state of the patient as well as with the physiological character of the respiration and the mechanical characteristics of the inspiration-time meter. Distribution curves of this type for physiological or psychodynamic studies can readily be obtained by having the patient breathe oxygen alone or physiological saline through the nebulizer. The device, therefore, is another way of studying the breathing pattern of the individual under conditions simulating aerosol therapy by the nasal route.

EXPERIMENTAL HISTAMINE ASTHMA

Data in the literature purporting to describe the comparative effects of therapeutic aerosols in a quantitatively evaluated fashion may often be erroneous. When three or four inhalations are given with the nebulizer and an aerosol is produced in the usual qualitative way for the patient to inhale, obviously only rough approximations can be given. Thus, in a recent paper which evaluates isopropyl epinephrine in comparison with other sympathomimetic amines, no quantitative data on inspiration is given and conclusions are open to serious question. The inspiration-time meter is designed to overcome errors of this type because it employs an essentially closed system. In any particular patient, the error will be fairly constant and dependent essentially on that produced by the loss due to deposition in the nose and oropharynx, provided the experimenter keeps other factors in mind. These factors are: (1) the particle size distribution, (2) the average inspiration time, and (3) the volume velocity with which a known quantity of the aerosol is administered and controlled. These factors can be reproduced fairly well in the same patient.

The following experiments with histamine aerosols are presented to illustrate the type of experiment which is possible with the inspiration-time meter.

Histamine diphosphate was dissolved in water containing 10 per cent of glycerine to bring it to the desired concentration. The glycerine was added to insure that the particle size distribution would remain fairly constant. As pointed out previously, 30 per cent glycerine was optimal, but it was decided that 10 per cent would suffice for the present experiments. In using a DeVilbiss No. 40 nebulizer and nasal tips with the L-tube (with vent open), a volume velocity of 7 to 9 liters per minute of oxygen was employed. In this early series the vent was kept open to facilitate the pa-

TABLE III. HISTAMINE AEROSOL

In all the experiments, the DeVilbiss No. 40 nebulizer was used with nasal tips and L-tube. The vent was open and the volume velocity was between 7½ and 8½ l/m oxygen (uncorrected). Three cubic centimeters of solution was the initial volume. The total inspiration time was 200 seconds unless otherwise noted. Experiments were done during the winter.

1	2.	3.	4. Average Vital Capacity in Cubic Centimeters (Three readings each)					5.	6.	7.	8.
Patient	Diagnosis	10% Glycerine Solution	Before Aerosol	After 50 sec.*	After 100 sec.*	After 150 sec.*	After 200 sec.*	Av. time of each inspiration in seconds	Number of inspirations	Total time of expt. in seconds	Symptoms
M.M.(1)	Ragweed Hay fever	1:5,000 Histamine	3700	3650	3700	3700	3500	6	32	—	None
(2)		1:500 Histamine	3480	3410	3650	3260	3580	8	25	—	Nose stuffy after 150 seconds
D.F.(1)	Asthma Allergy: Ragweed, etc.	1:5,000 Histamine	3100	1900	After 32 seconds heaviness in chest as in beginning of asthmatic attack. 0.2 c.c. epinephrine given. Vital capacity 10 min. later—3150**			1.3	17	—	**
(2)		Physiol. Saline	2460	2630	2480	2450	2580	2.5	80	337	None
F.R.(1)		1:5,000 Histamine	2570	2500	2800	2750	2800	2.0	101	374	Running nose no tightness in chest
(2)	Asthma when excited Dust-sensitive	1:500 Histamine	2350	2850	2600	2700	2750	3.5	57	302	Sneezing, Running nose
(3)		1:500 Histamine	2350	2700	2650	2600	2700	3.3	60	281	Running nose
H.K.(1)	Bronchial asthma Cor pulmonale	1:5,000 Histamine	710	After 16 sec. tightness in chest. Vital capacity—513 c.c.** Relieved with 0.2 c.c. epinephrine.				4	4	32	**

*Inspiration time in seconds.

tients' breathing. In subsequent experiments the vent was closed. The vital capacity was taken in triplicate with a Buhl spirometer before the experiment and then in triplicate at 50-second intervals. Asthmatic patients who responded, however, usually were unable to take the 200 seconds of inspiration time. If asthma or tightness in the chest occurred, the experiment was stopped, the vital capacity was taken and 0.2 c.c. of 1:1000 epinephrine solution by hypodermic injection was administered. If there were no untoward reactions to 1:5000 histamine, the patient was given 1:500 at a subsequent visit and not immediately following.

To illustrate the use of the inspiration-time meter in producing asthma with histamine aerosol, the type of data which may be obtained are given in Table III. Thus Patient M. M., who is a typical ragweed hay fever patient, was able to take during the winter, when these experiments were done, both 1:5000 and 1:500 histamine aerosols on repeated occasions for 200 seconds of inspiration time with no change in vital capacity. In addition, except for a stuffy nose there were no other symptoms. On Patient M. M. the average time of each inspiration varied between 6 and 8 seconds. Patient D. F., on the other hand, who had clinical asthma as well as sensitivity to ragweed, responded to 1:5000 histamine after 32 seconds with heaviness in the chest and a reduction in vital capacity from 3100 c.c. to 1900 c.c. Ten minutes after 0.2 c.c. of epinephrine was given, the vital capacity was restored to 3150 c.c. It is of interest that this patient must have retained comparatively much less histamine than Patient M. M., because the average inspiration time was only about 2 seconds. With so short an inspiration time (32 seconds) and with a volume velocity of about 8 liters per minute in the closed system which was employed, the patient can inspire only about 150 c.c. per second. This patient, therefore, on each inspiration inspires only 200 c.c. of a gas-oxygen-aerosol mixture under our conditions. Only a fraction of this volume reaches the recesses of the lungs. It should be noted that when physiological saline was used, the change produced by 1:5000 histamine is no longer observed, the average inspiration time increasing to 2.5 seconds with the inverse ratio of inspiration to expiration still prolonged. A rather interesting example is F. R., who has severe asthma especially under emotional stress. In this patient, although there were some nasal symptoms caused by the histamine, the 1:500 histamine on two occasions produced no decrease in vital capacity. The ratio of inspiration time to expiration time was, as found with our technic, higher than 0.5. This is evident from inspection of columns 4, 5, 6, and 7, with the ratios of 200 to 374, 302, and 281 seconds, respectively. Patient H. K. responded immediately to 1:5000 histamine. This patient with bronchial asthma and cor pulmonale was anoxic to begin with. Her vital capacity was 710 c.c. and dropped to 513 c.c. after 16 seconds of 1:5000 histamine. However, the patient recovered immediately following a small dose of epinephrine. Administration of epinephrine aerosol in this patient did not increase the vital capacity above 1000 c.c. The patient subsequently

made a fair recovery in an oxygen tent, the vital capacity still remaining below 1000 c.c.

In certain patients similar to patients D. F. in Table III, there is a marked change in vital capacity with few if any sibilant or sonorous râles appearing in the chest. In other words, histamine asthma is produced in all likelihood by spasm of the bronchial tubes having fairly large diameters. Histamine asthma of this type is similar to the preasthmatic sensation of constriction and heaviness in the chest so often complained of before the wheezing respiratory sounds are audible.

DISCUSSION

The method herein described has several defects which have already been noted. These are losses due to dispersion in the nasal passages, swallowing, and exhalation of particles. On the other hand, the advantages offered by the present technic are made clear by a closer scrutiny of the data in Table III. The subject breathed in 8 liters of oxygen per minute for an inspiration time of 8.33 minutes. We know, therefore, that the subject breathed 66.6 liters of oxygen and, therefore, of aerosol, during this time Since the average inspiration was 7.2 seconds, and since the subject breathed 136 c.c. of oxygen per second, each inspiration amounted to approximately 980 c.c. of the aerosol. In terms of delivery to the subject it is likely that at least 9 mg. of PSP were deposited in the lungs during sixty-nine inspirations, or about 0.13 mg of dye was available for passage through the lung barrier per average inspiration. It seems likely that the method, therefore, provides a controllable technic of studying lung clearance by means of determinations of the dye or of para-aminohippuric acid in the urine. It is believed that through study of the curve of urine values against delivery values, more precise data on the nature of the lung barrier and the effects of drugs on this barrier during aerosol therapy may be achieved. Blood values if obtainable would be preferable.

The variability in the response of asthmatic patients (to be described in a future communication) to histamine aerosol under those controlled conditions has led to the assumption that within the dose range established only certain asthmatics will respond to histamine with a diminution in vital capacity. Preliminary data indicate that asthma is more readily produced in individuals whose asthma is more closely connected with immunologic than with psychologic factors. Where emotional upsets produce asthma, as evidenced in our series thus far, histamine aerosol does not as readily produce a change in vital capacity. Although our data are insufficient, they, nevertheless, suggest that an unbalanced or sensitized bronchial tube is more sensitive to histamine and other spasm-producing substances and that this sensitivity is not as dependent upon the emotional pattern of the patient as upon the immunologic state of the tissues involved.

SUMMARY

1. A technique for measurement of the time taken for inspiring aerosols is described. The device consists essentially of an electric circuit-maker which is activated by the back pressure that is set up when the aerosol is inspired.

2. By this method (a) the total number of inspirations, (b) the average inspiration time, the total inspiration time, (c) the population distribution of inspirations, and (d) the ratio of the inspiration time to total time of respiration, are obtained.

3. A typical experiment on lung clearance of phenolsulfonphthalein aerosol as a function of inspiration time is given. It is shown that within the limits of experimental error, there may be a linear relationship between the weight of dye excreted in two hours and the inspiration time between 200 and 400 seconds. By this technique it is demonstrated that under certain conditions approximately 15 to 20 per cent of dye clears the lung barriers and is excreted in the urine.

4. Experiments on the production of histamine asthma with this technique provide a reproducible procedure for the induction of experimental asthma under semi-quantitative conditions and its control by therapeutic agents.

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133 East 58th Street

CLINICAL EXPERIENCE WITH CHLOR-TRIMETON IN HAY FEVER AND OTHER ALLERGIES

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THE high therapeutic index and low toxicity reported for the antihistamine, Chlor-Trimeton maleate,[2] brand of chlorprophenpyridamine maleate, prompted this investigation to determine its effectiveness in a variety of allergic disorders. Chemically the compound is 1-(p-chlorophenyl)-1-(2-pyridyl)-2-N, N-dimethylpropylamine maleate. It is the maleic acid salt of a new compound derived by halogenating the antihistaminic substance, Trimeton, brand of prophenpyridamine.

The clinical reports on Chlor-Trimeton maleate to date have shown it to possess high therapeutic efficacy and have confirmed its low toxicity in man.[1,3]

CLINICAL MATERIAL

In the present series Chlor-Trimeton maleate* was administered to 332 office patients. The patients sensitive to inhalant allergens were receiving standard hyposensitizing injections. The conditions from which they suffered were as follows: hay fever; hay fever accompanied by asthma; pollen, mixed and infective asthma; vasomotor rhinitis of allergic, infective, and of unknown origin; urticaria; and several miscellaneous affections potentially of allergic origin. All of the cases were seen in private practice, and the results were tabulated on several successive visits. Since many of the patients had more than one symptom picture, the tabulated results were observed in over 550 symptoms or syndromes.

DOSAGE

The dosage of Chlor-Trimeton maleate required to alleviate allergic symptoms appeared to be 2 to 4 mg. orally given from two to four times daily, with the usual dosage being between 6 and 20 mg. daily. In a variety of allergic disorders, Allison and Robinson[1] obtained satisfactory relief in twenty-six of thirty-six patients (72.2 per cent) with doses of Chlor-Trimeton maleate in this range three times a day. Vickers and Barrett[3] found the optimal dosage in seasonal hay fever to be 6 to 16 mg. per day in divided doses. In an attempt to determine the optimal dosage, 1, 2, 4, and 8 mg. three times daily were administered to eight, 157, 158, and nine patients, respectively.

TABULATION OF RESULTS

Table I records the results with these dosages in the various conditions. Strangely, there was no response in the nine patients in which doses of 8

*Chlor-Trimeton maleate was supplied by Schering Corporation, Bloomfield, New Jersey.

Presented at the Sixth Annual Meeting of The American College of Allergists, January 15-18, 1950, St. Louis, Missouri.

TABLE I. CLINICAL RESULTS WITH CHLOR-TRIMETON MALEATE IN ALLERGIC DISORDERS

CLINICAL RESULT: NUMBER OF CASES

Type of Allergy	No. of Cases	1 mg.			2 mg. q.i.d.			4 mg. t. or q.i.d.			8 mg. t. or q.i.d.		
		Good	Fair	Poor	Good	Fair	Poor	Good	Fair	Poor	Good	Fair	Poor
Hay fever, total	247	2	5		47	54	21	27	62	26			3
Hay fever with asthma	85	1	3		9	23	6	3	27	12			1

RESULTS—DOSAGE 2 TO 4 mg. q.i.d.

	No. of Cases	Good	Fair	Poor
Pollen asthma	29	10	12	7
Mixed (allergic and infective) asthma	66	2	52	12
Infective (intrinsic) asthma	46	0	9	37
Vasomotor rhinitis—allergic, infective, and unknown etiology	30	4	17	9
Angio-edema and urticaria	10	1	6	3
Eczema and dermatitis	16	0	1	15
Vertigo due to pollen	1	1	0	0
Migraine	4	0	1	3

Good: 75-100% relief of symptoms
Fair: 50- 75% relief of symptoms
Poor: 0- 50% relief of symptoms

TABLE II. ONSET AND DURATION OF THE EFFECT OF CHLOR-TRIMETON MALEATE

ONSET

Time in Minutes

Dosage	No. of Patients Reporting	15		15-30		30-60	
		No.	%	No.	%	No.	%
2 mg.	59	23	39.0	26	44.0	10	17.0
4 mg.	73	33	45.2	25	34.2	15	20.6

DURATION

Time in Hours

Dosage	No. of Patients Reporting	2-4		4-8		8-12		12-24		Over 24	
		No.	%	No.	%	No.	%	No.	%	No.	%
2 mg.	108	15	13.9	47	45.3	24	22.2	21	19.4	1	Less than one
4 mg.	92	17	18.5	34	37.0	27	29.4	13	14.1	1	1.0

mg. three times daily were tried. When symptoms disappeared completely following administration of Chlor-Trimeton maleate, that is with 75 to 100 per cent relief, the result was called good. When relief of symptoms was partial, from 50 to 75 per cent, it was recorded fair. Poor results were those in which less than 50 per cent relief or none was obtained.

ONSET AND DURATION

Fifty-nine of the 157 persons receiving 2 mg. of Chlor-Trimeton maleate per dose were able to determine the time of onset of the effect of the medication. Twenty-three (39 per cent) became aware of it within fifteen minutes, twenty-six (44 per cent) within fifteen to thirty minutes. Among those receiving 4 mg. per dose, a slightly higher percentage noticed the

TABLE III. COMPARISON OF RESULTS WITH DOSAGES OF 2 AND 4 MG. OF CHLOR-TRIMETON MALEATE

Type of Allergy	2 mg. t.i.d.					4 mg. t.i.d.				
	Total No. Cases	Improved		Not Improved		Total No. Cases	Improved		Not Improved	
		No.	%	No.	%		No.	%	No.	%
Hay fever, total	122	101	82.8	21	17.2	115	89	77.4	26	22.6
	2-4 mg. t.i.d.									
	Total No. Cases	Improved		Not Improved						
		No.	%	No.	%					
Pollen asthma	29	22	76	7	24					
Mixed (allergic and infective) asthma	66	54	81	12	18	Improved: 50-100% relief of symptoms				
Infective (intrinsic) asthma	46	9	20	37	80					
Vasomotor rhinitis	30	21	70	9	30	Not Improved: 0-50% relief of symptoms				
Urticaria	10	7	70	3	30					
All others	21	3	15	18	85					

effect within fifteen minutes. It appeared in approximately 80 per cent within thirty minutes. The effect was apparent in all patients reporting in both groups within an hour, as shown in Table II.

One hundred and eight persons receiving the 2 mg. dosage and ninety-two of those receiving 4 mg. reported the duration of the effect of Chlor-Trimeton maleate. There was no significant difference in the two groups, the effect with the 2 mg. dosage lasting as long as that with twice the amount.

The 247 patients with seasonal hay fever comprised the largest group treated. Among the 122 of them who received Chlor-Trimeton maleate in 2 mg. doses, 101 (83 per cent) showed improvement consisting of 50 to 100 per cent relief of the mucous membrane inflammation and nasal discharge characteristic of hay fever. Only twenty-one (17 per cent) showed no improvement. These percentages are slightly better than those obtained when 4 mg. were given to 115 patients in the hay fever group. Table III presents this comparison. Two hay fever patients received one mg. three times a day. One responded to this minute dose with complete relief of symptoms, the other with partial relief. In the former the antihistamine effect lasted for six to twelve hours. In the latter, appearance of the effect was delayed but it lasted for four to six hours.

As may have been expected, the asthmatics of the infective or intrinsic etiology were helped little or not at all by the drug. Among these nine (20 per cent) reported some degree of relief, while thirty-seven (80 per cent) reported little or no help. On the other hand, those asthmatics in whom extrinsic factors were wholly or partly responsible for their symptoms were benefited by the drug. Where the extrinsic factors were, as far as could be determined, the sole contributing cause, as in the pollen asthmatics, 35 per cent had good results, 41 per cent fair results and 24 per cent poor results from the use of Chlor-Trimeton maleate. Where the extrinsic etiological factors were accompanied by infection, the good results were only 3 per

TABLE IV. SIDE REACTIONS

	1 mg.		2 mg.		4 mg.		Total	
	Mild	Severe	Mild	Severe	Mild	Severe	Mild	Severe
Drowsiness	1		15	1	9	2	25	3
Vertigo			1		1		2	
Headache					1	1	1	1
Gastrointestinal upset					2		2	
Grogginess			1				1	
Lightheadedness			1				1	
Difficulty in focusing			1				1	
Diarrhea			1				1	
Listlessness			1				1	
Shakiness			1				1	
Nervousness			1				1	
Disturbing dreams			1				1	
Dry throat, cough					1		1	
Aggravation of chief complaint			1*		1**		2	

*Eczema.
**Hay fever with eczema.

cent, while the fair results were 78 per cent and the poor results only 18 per cent.

Considering all the cases of hay fever together, 101 (82.8 per cent) of the 122 receiving the 2 mg. dosage improved, as shown in Table III. Satisfactory improvement also was obtained with 4 mg. of Chlor-Trimeton maleate in eighty-nine (77.4 per cent) of the 115 receiving this dosage. It would appear, therefore, that the compound represents a highly effective agent for control of the symptoms of this allergic manifestation, and that a dose no larger than 4 mg. suffices to produce the effect.

Table III also shows the effectiveness of Chlor-Trimeton maleate in vasomotor rhinitis. The small number of patients warrants no conclusions, but improvement in twenty-one of thirty seems to indicate that it is effective. Concomitant rash and cough in two patients were not improved.

Too few persons with urticaria, eczema, dermatitis, or migraine presented themselves for an accurate evaluation of the worth of Chlor-Trimeton maleate in these disorders. Four mg. brought partial relief of itching and partial disappearance of the eruption in seven persons with urticaria. Fifteen with eczema or dermatitis and three with migraine showed little or no improvement.

SIDE REACTIONS

Thirty-six mild reactions occurred in the series, an incidence of 10.8 per cent. The most frequent reaction was slight drowsiness which followed the administration of 2 mg. in fifteen persons, and the administration of 4 mg. in nine. One in the 2 mg. group also experienced vertigo, and this reaction occurred once with the larger dose. Two persons receiving 4 mg. had a gastrointestinal upset. Other mild reactions occurred one time each.

Of the four persons treated who had more intense reactions to the drug, headache forced one to discontinue its use. The other three were very

(Continued on Page 327)

THE ANTIHISTAMINIC DRUGS

Their Relationship as Shown by the Structural Formulas

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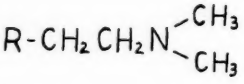
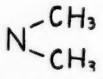
IN THE PAST three years an even dozen antihistaminic drugs have been placed on the market for the control of allergic symptoms. The purpose of this paper is to emphasize their relationship as shown by their structural formulas.

The structural formula common to almost all of them could be represented as follows:

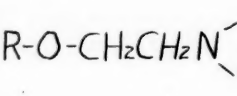
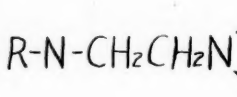
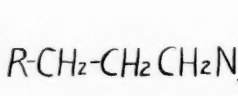


Here R is any large slightly basic radical representing 75 per cent of the molecular weight of the compound. The



does the blocking of the histamine from the receptor positions in the tissue cells. Hence this dimethyl amino group gives the maximum antihistaminic activity attained by the compounds so far discovered. Efforts to improve the action of the compounds by changing the side chains of the carbon atoms of the ethylene groups have not been practical. Therefore this part of the formula has remained the same in eleven of the antihistaminic compounds.

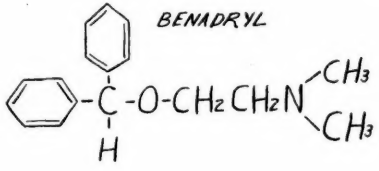
The first differentiation that has been made is in the first atom attached to the etheylene radical, as shown by these examples:

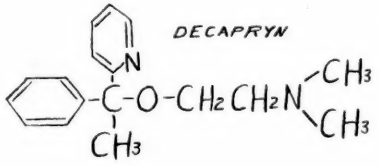
	DROWSINESS	ACTIVITY	TOXICITY
	1	1	2
	2	2	1
	3	3	3

Presented at the Fifth Annual Meeting of The American College of Allergists, April 14-17, 1949, Chicago, Illinois.

Here we see that comparing the three types of compounds the attachment of an atom of oxygen causes the greatest toxicity and drowsiness and is second best in antihistaminic activity in animal experiments. The attachment of an atom of nitrogen results in the best antihistaminic activity and causes less toxicity and drowsiness. The attachment of a methyl radical gives the third best antihistaminic activity and causes the least toxicity and drowsiness.

The two commercial compounds having the oxygen atom attached to the dimethyl amino ethylene are Benadryl (dimethyl amino ethyl benzohydryl ether) and Decapryn (dimethyl amino ethyoxy methyl benzyl pyridine). Hydrillin is a Benadryl base combined with aminophylline.



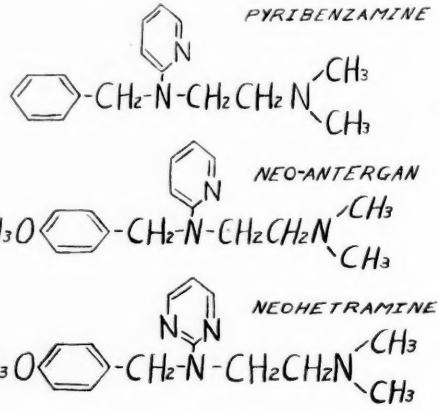


By animal experiment these two compounds, as would be expected by the slight difference in their structural formulas, are very similar in activity, but Decapryn is also more toxic on animals though it causes less sedation. Clinically the Decapryn seems to be effective in smaller doses, and therefore the side reactions are less likely to be important.

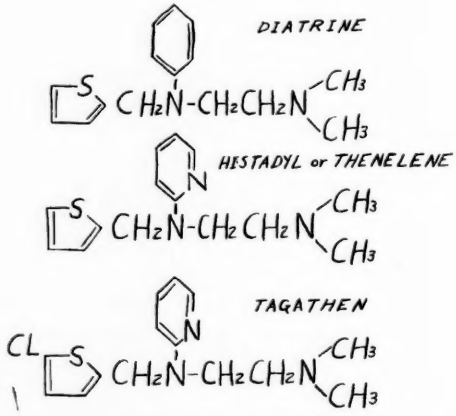
The large group of six compounds having a nitrogen atom attached to the dimethyl amino ethylene are divided into two groups of three each. The first group has a benzl radical as part of the large R radical. This benzyl group increases basicity of the large R about 300 times. The three compounds are Pyribenzamine [N (2 pyridyl) N (benzyl) N′ N′ dimethyl ethylene diamine], Neo-Antergan [N (methyoxybenzyl) N (2 pyridyl) N′N′ dimethyl ethylene diamine], and Neohetramine [N (methoxybenzyl) N (2 pyridimidyl) N′ N′ dimethyl ethylene diamine].

When compared by animal experimentation, the addition of the methoxy group to the benzl radical markedly improved the antihistaminic activity of the compound. However, clinically there is often little difference between the action of Pyribenzamine and Neo-Antergan.

The substitution of the pyridimidyl group for the pyridyl group, as in Neohetramine, reduces the antihistaminic activity on animals but lowers the toxicity also. Clinically this drug is not as potent as the two previous compounds but it also has fewer side reactions.



The second group of compounds having a nitrogen atom attached to the dimethyl amino ethylene has a 2 thenylmethyl group attached as part of the large R radical. Chemically and by animal experiment and clinically this does not appear to make much change in the reactions of the compounds. The three compounds are Diatrine [N (phenyl N (2 thenyl-



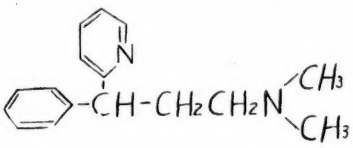
methyl) N′ N′ dimethyl ethylene diamine], Histadyl or Thenylene [N (2 pyridyl N (2 thenylmethyl) N′ N′ dimethyl ethylene diamine], and Tagathen [N (2 pyridyl) N (2 thenyl 3 Cl methyl) N′ N′ dimethyl ethylene diamine].

The substitution of the 2 pyridyl group for the phenyl group, as in Histadyl, increases the animal-tested antihistaminic activity of the compound and also seems to make it more potent, clinically. However, it also may increase the side reactions.

In Tagathen, the addition of the chlorine radical to the thenyl methyl group doubles the antihistaminic activity of the compound in animal tests. However, in its clinical activity it is very similar to the compounds like it without the chlorine added.

There is only one commercial drug where the large R radical is attached to the Dimethyl amino ethylene by a methyl group. This is Trimeton [1 phenyl 1 (2 pyridyl) 3 dimethyl amino propane].

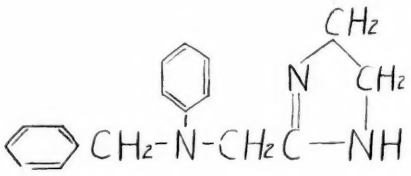
TRIMETON



This compound is not as active by testing on animals or clinically in the role of an antihistaminic as either of the other two groups of compounds with the nitrogen or oxygen attached to the dimethyl amino ethylene. However, it is also neither as toxic nor as likely to cause drowsiness. In fact in some patients it may be stimulating.

One of the oldest antihistaminics that is not nearly as active either on animals or in clinical use is Antistine (2 phenyl, benzl amino ethyl imidazoline).

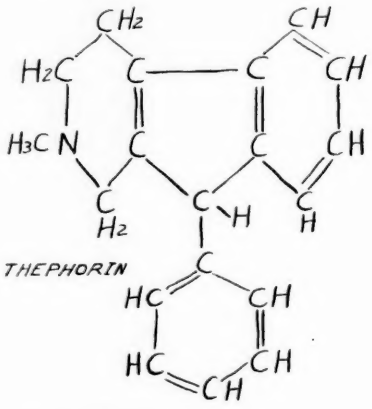
ANTISTINE



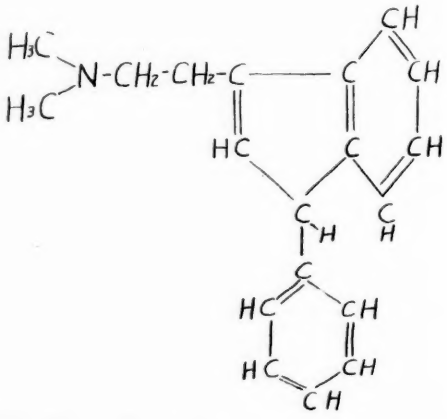
By animal experimentation this compound is very weak compared to all the others. When used clinically, even when used in double the dosage, it does not compare favorably. However, it is not irritating when used locally in the nose or eyes, and for that reason it is at times useful. Its best results, when compared to other drugs, are in the relief of urticaria, where it seems to be quite effective if the dosage is large enough. It produces wakefulness as a rule and not sedation. This compound does not

contain the dimethyl amino group as such, but probably the imidazoline hydrolizes to produce it in the tissues.

The last of the commercially available antihistaminics by its structural formula is quite different from the others. It is Thephorin (2 methyl, 9 phenyl, 2, 3, 4, 9 tetrahydro, 1 pyridindine).



It is easy to see how this compound could break down in the tissues to form a dimethyl amino ethylene by breaking the ring where the nitrogen is found. We now have the following compound:



This drug is as effective by animal experimentation as most of the others. It is also quite useful clinically. The greatest advantage in its use is in those patients in which the other antihistaminics produce drowsiness. This compound's most troublesome side reaction is nervousness.

We thus find that we have available four groups of compounds: first,

Benadryl, Decapryn and Hydrillin; second, Pyribenzamine, Neo-Antergan and Neohetramine; third, their close relatives, Diatrine, Histadyl or Thenylene, and Chlorathen; and fourth, the miscellaneous group, Trimeton, Antistine and Thephorin. By an understanding of the relationship by chemical formula of these compounds we can use them more intelligently. Clinical experience has shown us all that patients not relieved sufficiently by one of them will often receive satisfactory relief from some other one; also, that side reactions that prevent entirely the use of one may be absent or tolerated when another type of drug is used. Therefore they should be tried out by first using one in each group. If relief is obtained but the side reactions are too severe, one should change to another less toxic drug in the same group. If not sufficient benefit is obtained, one can change to another group. The miscellaneous group is especially useful in those patients where the other drugs produce marked drowsiness.

817 Third National Building

CHLOR-TRIMETON IN HAY FEVER

(Continued from Page 321)

drowsy, two of them with the 4 mg., one with the 2 mg. dosage. This represents an incidence of more intense reactions of 1.2 per cent. Eight persons discontinued the drug because of their reactions, an incidence of 2.4 per cent. Of these, six had previously been unable to tolerate other antihistaminics. The other two were able to tolerate alternate drugs. The remaining 324 persons continued the use of the drug. Their toxic symptoms either disappeared after the first day of use of Chlor-Trimeton maleate or were so mild as to be inconsequential. Almost all of the cases in whom drowsiness was experienced had had similar effects from other antihistaminics.

SUMMARY

Chlor-Trimeton maleate is a highly effective therapeutic agent, especially useful for the symptomatic relief of hay fever alone or accompanied by other allergic manifestations. It is effective in a dose of 2 to 4 mg. three times daily. Results with the smaller dose appear to be adequate in about half of the cases. Chlor-Trimeton maleate possesses an extremely low toxicity and is likely to cause no more than 3 per cent severe side reactions.

170 Maple Avenue

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DENERVATION OF THE LUNGS FOR BRONCHIAL ASTHMA

Case Report

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Toledo, Ohio

SURGERY is finding a place in the treatment of severe cases of intractable bronchial asthma. There is enough experimental and clinical evidence to show that removal of the nerve supply to the lung has a sound basis in the treatment of bronchial asthma.

In 1929, Phillips and Scott wrote a comprehensive paper on the surgical treatment of bronchial asthma. They discussed the rationale of this treatment and the various surgical procedures that had been used.

In 1942, Rhienhoff and Gay reported a total of twenty-one cases treated by bilateral resection of the posterior pulmonary plexus. The operation consisted of exposing the vagus nerve through an intrathoracic approach and cutting all the fibers to the lung. In addition, the areolar tissue of the hilus was cleaned off the bronchus and the pulmonary vessels in order to remove all nerve fibers entering the lung. Of this group, eight patients were dramatically relieved of the asthma.

In 1948, Carr and Chandler reported the treatment of intractable asthma by doing a bilateral dorsal sympathetic ganglionectomy. They reported five patients treated by this method whom they had observed from four to ten years. All of these patients, who had been totally incapacitated, obtained enough relief to be able to return to work.

In July, 1948, Brian Blades reported four cases of intractable asthma relieved by unilateral denervation of the lung. The operation consisted of a transthoracic resection of the branches of the vagus nerve to the lung and the removal of the areolar tissue around the hilus of the lung. He cleaned as much of the tissue as possible off the pulmonary vessels and bronchus in order to destroy any invisible fibers entering the lung. He chose the left side because of the greater abundance of autonomic nerves on the arterial side of the chest.

Two types of operations are described in these reports. In one operation, the upper dorsal sympathetic ganglia are removed extrapleurally on both sides. In the other operation, the vagus fibers entering the lungs are removed through a transthoracic approach. Anatomic and experimental evidence indicate that resection of the vagus nerve fibers to the lung is the better of the two operations.

A review of the clinical and experimental work on asthma reveals the following points:

1. That the state of asthma is due to spasm of the bronchi, swelling of the bronchial mucosa and an increase in bronchial secretions. Any one or all of these factors may be the cause of the asthma.

2. That the extrinsic nerve supply of the lung is derived from the sympathetic and vagus nerve fibers. These fibers are arranged about the posterior surface of the hilum of the lung to form the posterior pulmonary plexus.

3. That the normal state of the bronchial tree (tone, bronchial mucosa and secretions) depends on a balance between the sympathetic and vagus nerves to the lung.

4. That both the sympathetics and vagus contain motor and sensory fibers.

5. That the vagus contains mostly bronchoconstrictor fibers, and that the sympathetic system contains mostly bronchodilator fibers.

6. That a reflex arc exists through the sympathetics and vagus. By interrupting the nerve pathway, the asthmatic attack can be prevented. This is the rationale of surgical denervation of the lung.

CASE REPORT

Case 1.—V. M., a white woman, aged thirty-four, developed a severe "chest cold" in the fall of 1943. Along with this cold, she had her first attack of asthma. Ever since then she had asthmatic attacks that increased in duration and frequency. During the past two years she had been in a state of intractable asthma. Her periods of relief from asthma never lasted more than three or four hours. The patient was totally incapacitated because of the asthma. It was practically impossible for her to leave the house. In 1943, a complete examination including skin tests was done by a competent allergist. The only allergy that manifested itself was sensitivity to iodides. The patient failed to improve under treatment. In 1944 she went to Tuscon, Arizona, where she remained for three months. She also visited California. However, she experienced no relief in these climates. In 1946 the patient entered a well-known university medical center. Complete studies, including a psychiatric examination, were done. The psychiatric examination failed to reveal any psychogenic basis for the asthma. A final diagnosis of intractable intrinsic asthma was made. Treatment was instituted. However, the patient failed to improve. In 1947 she was treated by a course of deep x-ray therapy over her lungs with no response. All types of medical treatment were tried with no avail. Aminophylline, adrenaline and aerosol penicillin were used frequently. However, the asthma became progressively worse.

Examination in May, 1948, revealed a thin white woman in a state of asthma. Auscultation of the lungs revealed the typical long expiratory wheeze of asthma. The rest of the examination by systems was essentially negative. X-ray of the lungs revealed increased bronchovascular markings in both lung fields. Bronchoscopy on two occasions revealed a hyperemic mucosa and viscid mucoid secretions in both bronchial trees. There was a marked expiratory intrusion of the posterior bronchial wall into the lumen.

On July 21, 1948, a thoractomy was done by resecting the fifth rib on the left side; denervation of the lung was performed. The vagus nerve was exposed by blunt and sharp dissection from the level of the aorta to the diaphragm. The nerve was elevated from its bed and all branches entering the lung were severed between ligatures. There were two branches along the superior aspect of the pulmonary artery. There was another branch originating from the recurrent laryngeal nerve that coursed along the anterior surface of the pulmonary artery. The largest branch that was severed passed along the posterior surface of the main stem bronchus. One branch passed behind the superior pulmonary vein, and two branches were found

along the under surface of the inferior pulmonary vein. Several minute branches could be seen going into the hilus of the lung. A few other very small branches were severed as they crossed through the posterior mediastinum to the other side. The inferior pulmonary ligament was divided up to the inferior pulmonary vein in order to eliminate any fibers that might be coming from the contralateral side. As much of the tissue as possible was cleaned off of the bronchus and the pulmonary vessels. The mediastinal pleura was then interposed between the nerve and its bed in the mediastinum. The pleural cavity was closed in layers.

The patient's response to this operation was dramatic. She experienced immediate relief of her asthma and remained free of asthma during her entire hospital course. She was discharged on the ninth postoperative day. The patient was free of asthma for one month. However, her attacks started to recur at this time. On September 16, 1948, a denervation of the right lung was performed. Again she was dramatically free of asthma for about one week. However, she continued to have periodic attacks of asthma for another two months which gradually decreased in severity and frequency. During the past three months the patient has been free of asthma. She experiences periodic "choking-up" sensations which are relieved after bringing up secretions from deep in her bronchial tree. Since her last operation she has done things which she had been unable to do for years, such as, lie flat in bed, go shopping downtown, go to the movies and go to a dance. At present she is seeking work as an office stenographer.

NOTE: Twelve months have elapsed since the last operation, and the patient is still free of bronchial asthma.

SUMMARY

1. Anatomic and physiological studies reveal that the extrinsic nerve supply of the lung is derived from the sympathetic and vagus nerves.

2. Clinical and experimental evidence is accumulating to indicate that removal of the nerve supply to the lung has a sound basis in the treatment of intractable bronchial asthma.

3. When all types of standard medical therapy fail in the treatment of bronchial asthma, surgical therapy should be given consideration.

4. A case is presented in which dramatic relief from intractable bronchial asthma was obtained following denervation of the lungs.

5. A final interpretation of the value of denervation of the lungs for asthma cannot be made until further experimental and clinical work has been done.

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MULTIPLE TESTING BY ELECTROPHORESIS

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THE introduction of chemical materials into the skin by means of a galvanic current has been practiced for many years and with many substances.[1]

Notably, in the field of allergy, the local administration of histamine and epinephrine by electrophoresis was reported by Abramson in 1938 and 1939.[2,3,4] In the latter year he reported the introduction of ragweed pollen by electrophoresis for both diagnosis and treatment. In his article Abramson states:

"A new way of studying allergic skin reactions may develop from recent experiments on the electrical introduction of the extracts of ragweed pollen into the human skin. . . . It would be a great advantage in the study of the allergic patient if tests could be made by placing the allergenic material directly on the unbroken skin.

"The advantages of using a method in which the skin is left intact are those connected with the elimination of obscurity produced by tissue injury, and the advisability of having a minute amount of the powerful allergenic material introduced at a very slow rate at the same skin level. It has now been found that active constituents of extracts of ragweed pollen which have been dialyzed to remove substances of low molecular weight can be driven electrically into the skin by the phenomenon of electrophoresis.

"Although the method of eliciting skin reactions to allergens by electrophoresis is still experimental, a rather wide field of investigation is opened up. There are innumerable substances which would be of interest to study: the pollens of the trees, other grasses, dusts and other inhalants, such as danders, perfumes, et cetera, as well as foods. In addition it would be very important to ascertain if certain substances which are used in patch-testing would give accelerated reactions or different reactions if introduced by electrophoresis."

In 1940 Dutton[9] expanded the method by skin testing with twenty kinds of pollen extracts and with foods, epidermals, and miscellaneous substances. He developed an apparatus with ten positive leads, each with its own milliammeter and rheostat. He stated:

"The skin reactions obtained by this method are quite similar to those obtained by scratch or intradermal testing, with flushing surrounding a definite wheal. Sometimes there are multiple papular points in the center of the reddened area which do not coalesce. In control reactions and negative reactions there is no evidence whatsoever of change in the skin. We have, therefore, been led to adopt the tentative interpretation that reddening without papule or wheal formation is a weak positive reaction. . . . We have come to believe that tests by this method more closely parallel actual clinical sensitivity than do tests by other methods."

Interested in the possibility of dividing the active allergen carrying electrode so that multiple testing might be carried out with a single lead, an apparatus was finally developed which seemed to solve this problem. The

active electrode consists of a flexible sponge rubber pad, approximately one-half inch thick, in which are imbedded small sockets. These sockets are connected in series by fine, flexible wires. Into these sockets are screwed plastic cups by means of a metallic stud which forms the base of the cup.

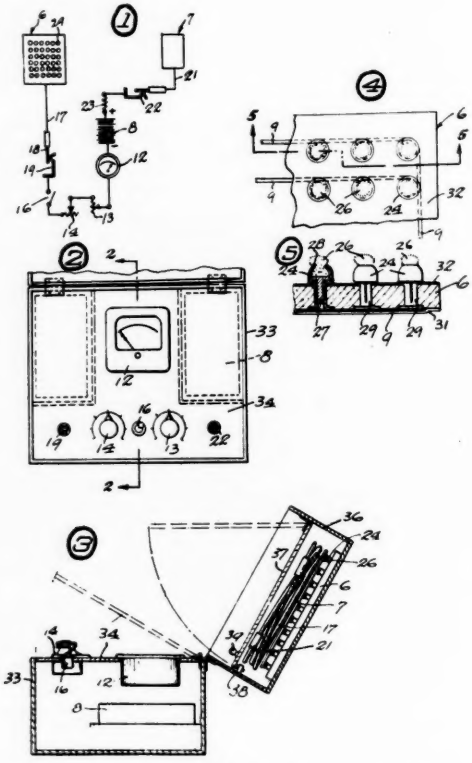

Fig. 1. (1) An electrical wiring diagram of the apparatus. (2) A layout showing the panel arrangement and the controls. (3) A section of the apparatus through line 2—2 of (2). (4) A partial top view of the flexible pad. (5) A section of flexible pad and cups showing cotton balls.

In operation each of the cups contains a small cotton ball which is saturated with an extract to be used in the test, the extract thus coming in contact with the metallic stud. The pad in use by the author at the present time contains sixty-six cups, although any number can be used, each having an effective area of approximately 0.5 square centimeter.

The active electrode is connected to the negative pole of a simple galvanic apparatus, receiving its current from two forty-five volt "B" batteries. The indifferent electrode is a small sheet of zinc which, in use, is wrapped with a wet towel and connected to the positive pole. Suitable rheostats for

coarse and fine adjustment of the current and a milliammeter complete the apparatus (Figs. 1 and 2).

As Dutton pointed out, "The most important (problem) probably centers around the type of extract to be used. . . . The pH, the presence of

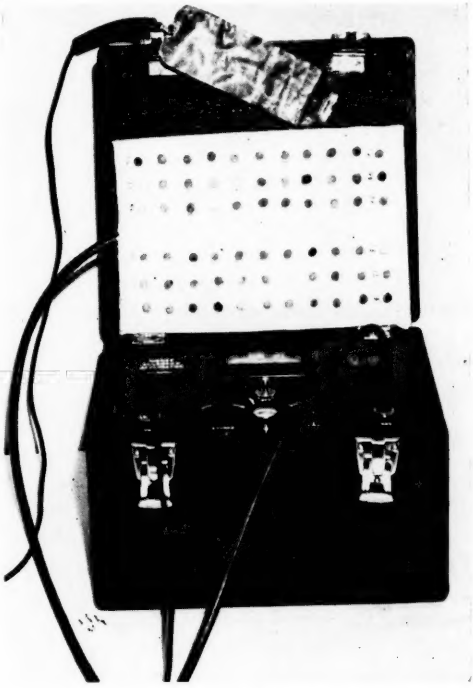

Fig. 2. A photograph of the apparatus.

electrolytes, and the concentration of the substances in solution, all have a highly important bearing on the production of sufficient mobility of the substance to insure that adequate amounts enter the skin." He found that in using aqueous extracts he obtained considerably more penetration, as evidenced by the size of the resulting wheal. My own experiments have borne this out, but in actual testing with pollens glycinerated extracts have proved to be satisfactory.*

In testing practice the patient is placed prone on a table with the back and chest bare. The back is prepared by lightly scrubbing with ether to remove the natural oil from the skin. The indifferent electrode (zinc plate) covered with a wet towel is placed beneath the chest and the lead connected to the positive pole of the apparatus. The flexible pad is placed on the patient's back and held in place by light sand bags. The lead from the pad

*Glycinerated extracts 1:20, prepared by Hollister-Stier Laboratories, are the ones used.

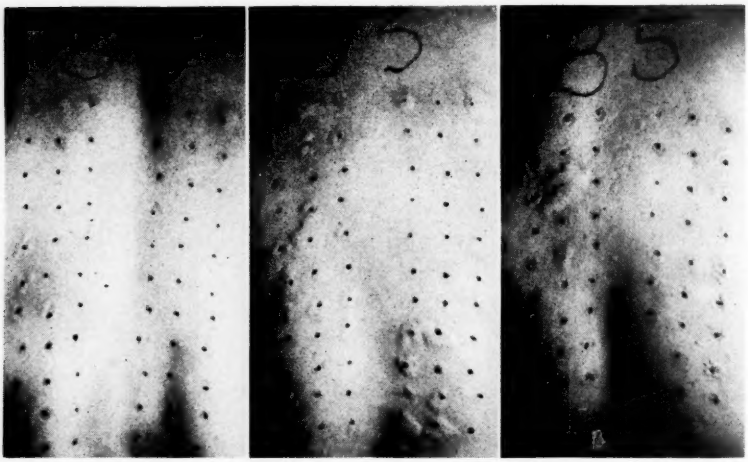

Fig. 3. (left) A photograph of a tested area showing several small reactions. The dark spots in the photographs are ink dots to show the location of the contact points and are not used in routine testing.

Fig. 4. (center) A similar photograph showing many 3-plus and 4-plus reactions.

Fig. 5. (right) A similar photograph showing a very large reaction.

is connected to the negative pole. Care is taken that each of the cups is in contact with the skin. The current is gradually increased to 0.05 milliamperes for each cup in use, or a total of 3.3 milliamperes for sixty-six cups. The pad is left in place with the current on for fifteen minutes. At the end of this time the current is reduced, turned off, and the pad removed. The results of the tests may be read immediately. Positive reactions are such as have been described by Dr. Dutton (Figs. 3, 4 and 5).

For convenience in recording the intensity of the reactions, an area of simple erythema is recorded as 1-plus; small, isolated, papular hives, 2-plus; coalescing hives, 3-plus; a large wheal with pseudopodia, 4-plus.

In operation, the method is entirely without discomfort, the patient experiencing a mild tingling sensation as the current is increased. As the test progresses, the patient often notices itching of various intensity about some of the contact points on the skin.

It has been found that several successive patients may be tested without the further addition of extracts to the cotton-containing cups and that the pad may be stored for several days between tests without the addition of extracts. With reasonable care in placing and removing the pad there is little likelihood of cross-contamination. If cross-contamination has occurred, the cotton balls are removed from the cups, the cups removed from the pad, cleaned, filled with fresh cotton, and moistened with extract. The extract-containing cups are so arranged on the pad that they correspond to a chart listing the allergens in use. This greatly facilitates recording the results. In spite of a large number of pollen extracts applied simultaneously

and the occurrence of many strongly positive reactions, constitutional reactions have never been observed.

As the method is entirely without discomfort, it is particularly helpful in testing small children. Occasionally, in patients with the dry, atrophic skin of the aged, tests have been negative where intradermal tests were positive.

Positive reactions have been obtained with dust, silk, and other inhalants, and with numerous food extracts, but the author feels that food extracts have not been sufficiently concentrated to give dependable results by this method. Much experimental work remains to be done to realize fully the possibilities of this method.

SUMMARY

1. A brief review of the history of testing by electrophoresis has been given.

2. An apparatus for and technique of multiple testing by electrophoresis has been described.

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Plan now to attend the Seventh Annual Congress of The American College of Allergists February 11-14, 1951, to be held at the Edgewater Beach Hotel, Chicago.

ALLERGY AND THE HEART IN CLINICAL PRACTICE

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THERE are few who debate any longer the question of allergic tissue responses. The works of Rich[8] and his collaborators, of Criep,[1] Selye,[9] and others, leave little doubt that cellular injuries may be produced and reproduced in specifically sensitized tissue by the repeated exposure to the specific antigen or hapten, be it food or inhalant, chemical or bacteria. Clinical symptomatology depends and follows upon the site or organ involved in the reaction. The symptoms may be primarily or secondarily the result of the lesion produced. Such lesions may be completely reversible, or lead to necrosis and ultimate cicatrix.[3] The cardiovascular system may be the not infrequent major shock organ in such a chain of events. This has been demonstrated by recent experimentations and clinical case reports.[5,6]

Our attention has been engaged by clinical syndromes involving the heart, either by connotation or by direct reference. The public as well as our profession has been made acutely aware of diseases of the heart and blood vessels, and frequently both patient and physician are led into the too easy assumption that the complaint is a cardiac ailment. We hope to show that much care is needed in confirming many of these diagnoses, and that a high index of suspicion for allergic factors may be the means of avoiding tragic repercussions for the patient and his family, to say nothing of the social and economic importance of the entire problem.

At the outset it must be stated that these cases are not in every instance definitive. The allergic patient grows old and develops the vascular changes of age with all of its implications and accidents. The role of allergic sensitization may be very slight, perhaps the minutest precipitating factor—one difficult to prove. On the other hand we know from the work of Katz[4] and his group that the coronary circulation goes into spasm on infusion of these vessels with foreign blood. They speculated on the relationship of this phenomenon to the entrance into the human blood stream of foreign proteins which might reproduce the conditions of the experiment. Such spasm was thought to "explain some cases of acute coronary insufficiency and angina pectoris, especially if the coronary vessels are already the seat of narrowing in the larger channels. Vasoconstriction affecting the smaller arteries under these circumstances would increase the resistance to flow in the already narrowed coronary bed." Wilcox and Andrus[11] had already shown that coronary constriction occurred in the isolated guinea pig heart following the administration of the protein to which the animal had been previously sensitized. These pure laboratory states probably never exist in man, any more than the so-called "heart-lung preparation." However, two cases of aspirin allergy which have come to our attention perhaps

Presented at the Fifth Annual Meeting of The American College of Allergists, April 14-17, 1949, Chicago, Illinois.

very nearly approximate a direct action on the heart, although there were other extracardiac effects. In each instance there were striking immediate conduction and rhythm changes, and in one a coronary occlusion with myocardial infarction from which a rapid and complete recovery ensued.

Quintero and Feros[7] studied electrocardiogastrographic changes in allergic reactions considered principally to involve the stomach. They demonstrated galvanometric changes due to milk, chicken, potato, and egg in specifically sensitive patients. Histamine likewise was shown to produce significant alterations in the base-line curve. Zivitz and Oshlag[12] report the case of an allergic subject with eosinophilic pleural effusion and pericarditis with effusion which they considered allergic in origin even though they did not feel they had adequate substantiation. Instances of allergic reactions affecting the cardiovascular apparatus abound in the literature,[10] and further interest in the subject has been aroused in connection with the "alarm" reaction of Selye.[9]

The *indirect* effects are so devious as to merit more lengthy discussion. The association of gaseous indigestion, swelling of the stomach or other hollow viscera, with heart pain is a commonplace. Its mechanism has been studied in several ways. The experience of Gilbert, Leroy et al[2] on dogs in which balloon distention of the stomach was produced and correlated with coronary flow showed a reduction in flow following increase of pressure, more marked when the distention involved the cardiac end of the stomach. Functional disorders of the stomach consequent to pylorospasm and gastric distention almost exactly reproduce this experimental condition. These investigators further showed in humans that anoxia produced cardiac pain more readily after feeding than when fasting, and that such effect could be generally prevented by atropine. They felt that the so-called indigestible foods were more apt to produce cardiac symptoms than the less irritating foods.

Yet it is not enough to prescribe digestible foods without being reasonably sure that allergenic foods, if determined at all, are excluded from the diet. Not infrequently such bland foods as milk, eggs and fruit juices act on an individual allergically sensitive to them, as an irritant or an indigestible. The net effect of these on the stomach, once ingested, is the clinical duplication of the experimental work outlined above with a similar adverse reflex action on the heart (Case 1).

Emotional factors affecting visceral tensions are likewise generally accepted as important in precipitating heart symptoms. In some allergic individuals the only subjective effects noted in the earliest or beginning allergic response are heightened nervous and emotional tensions (Case 2). Indeed it is quite likely that vital medullary centers are so involved. In excessive or very heightened responses, syncopal seizures may follow with drop in blood pressure to shock levels. Individuals in the atheromatous age group may then suffer genuine myocardial necrosis due to the ensuing anoxemia, a coronary accident in no wise as serious in import as the so-

called primary coronary thrombosis. We have seen several cases in this category, one in a patient allergic to Roquefort cheese. Serial electrocardiograms showed changes that were "minimal but definite," and quick and uneventful recovery followed.

Heart failure as observed clinically may not always represent the gradual weakening of a damaged or overworked muscle. Frequently this condition is precipitated by the wildest series of extrasystoles and conduction changes (Case 3). Generally accepted cardiac management is promptly instituted in every instance. However, in our experience, those patients who are found to have food allergies recover compensation more quickly on an exclusion type diet (eliminating observed offenders often found to have been a prominent precipitating factor). They can usually be restored to a circulatory status superior to that prior to the failure episode. It has been noted again and again that their resilience is greater, and the recovery prompter and firmer (Cases 4 and 5).

We cannot feel that the criterion of a single food causation need be invoked in this group of cases, nor that the condition need be reproduced by feeding the interdicted food or foods. The complexities of factors in vascular allergic manifestations tend to obscure the cause-and-effect relationships. These have been critically reviewed by Miale,[6] with the conclusion that a too simple application of Koch's postulates is not valid, much less necessary. The human experiment in clinical practice cannot be laboratory-wise controlled, nor could we risk the reproduction of the acute heart failure episode in most of these cases. The program is simply *one* of the several efforts directed at a *heart-sparing regimen*. One is forced to rely on the hazardous criterion of clinical results.

Children with cardiac murmurs brought to Florida because of persisting symptoms thought to be due to the rheumatic state occasionally continue with these complaints until their true nature is elucidated (Case 6). In this group once the allergic etiology is found and treated, all evidence of the former disabilities may disappear. Some children are put at bed rest for many weeks because of aches and pains in the legs, low grade fever, and a cardiac murmur. Time and salicylates work no cure, and harassed parents and child seek other explanations. These are the patients who similarly reward the curiosity of the allergy-minded physician, and at the same time have removed from themselves a diagnosis of considerably graver prognostic import.

The general concern over substernal and precordial pain emphasizes the need for careful differential diagnosis, especially when there is slight shortness of breath (Case 7). The subasthmatic seizure must be considered if the victim is to avoid being mislabeled a cardiac. The frank outspoken attack of asthma can be recognized by almost any observer. Between normal respiration and full-blown asthmatic breathing there can be every possible gradation of respiratory difficulty or awareness, both subjective and objective. This possibility must be explored in the resolution of any cardiorespiratory complaint that defies definitive diagnosis (Cases 8 and 9).

CASE REPORTS

Case 1.—Mr. Wm. G., aged sixty-five years, was seen first because of pain in chest radiating down left arm, and shortness of breath. Two nights previously he ate some peanuts, and several hours later developed nausea with stomach-ache. He then suddenly developed severe pain in precordial region running transversely through his chest and into both arms. The pain eased somewhat and he slept fitfully that night.

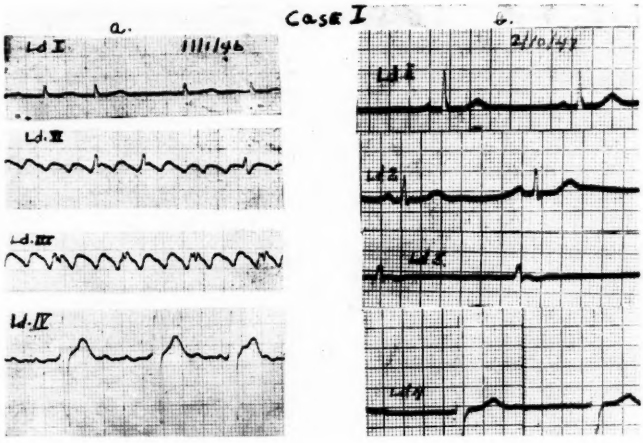

Fig. 1. Case 1. (a) Auricular flutter, varying block. No evidence of posterior coronary thrombosis; proven on serial electrocardiograms. (b) Normal sinus rhythm.

Dull precordial pain persisted the next day, and he noted that his heart seemed to race in irregular fashion. He was seen by his physician that evening and hospitalized because of auricular flutter with possible coronary infarction, posterior in type.

Further history revealed "biliousness" with frequent association of spots before the eyes and dizziness, much bloating and constipation.

It was most difficult to abolish the auricular flutter mechanism, but the patient was clinically relieved and ambulatory following the establishment of A-V block with slowing of cardiac rate to 66 per minute. There was no evidence of coronary thrombosis. In the next few weeks, without change in medications, the A-V block varied with periods of more rapid heart rate following "gaseous" indigestion and food upsets. Many food intolerances were noted, many of which could not be classified in the usual "undigestible" food groupings.

The auricular flutter was eventually abolished and the electrocardiogram revealed a normal tracing with regular sinus rhythm. Two years later patient continues to do very well; he states he is still adhering to allergic food eliminations from diet. He reports that he occasionally gets "spots" before eyes and dizziness and extra heart beats when he becomes careless with his diet in regard to allergies (Fig. 1).

Case 2.—Mr. W. W. L., a retired consulting engineer, aged fifty-eight, had a history of frequent attacks of paroxysmal tachycardia of one year's duration. He had had mild spells of cardiac extrasystoles for forty-two years, but the recent attacks had been incapacitating. Patient had noted that his seizures were always worse with excitement or nervous strain. Hence, his medical treatment had always been directed along these lines employing bromides, phenobarbital and quinidine as necessary. Of

late he had been forced to cancel several guest speaker commitments because of inability to prevent attacks in spite of medication up to tolerance.

Further history revealed so-called "chronic appendicitis" and "chronic G.B. disease," frequent occipital headaches, chronic sinusitis and laryngitis. Digestive inquiry indicated dysphagia when working hard, occasional heartburn and sour regurgitation one hour after meals. The patient observed food idiosyncrasies to

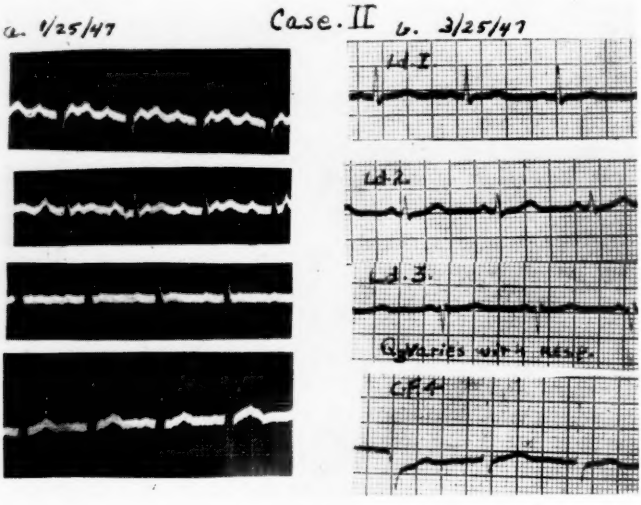

Fig. 2. Case 2. (a) Paroxysmal tachycardia; auricular flutter type. (b) Normal sinus rhythm; no evidence of myocardial damage.

bananas, cheese, tomatoes, chocolate and eggs. At time of examination his cardiovascular status was essentially normal, with regular sinus rhythm, a blood pressure of B.P. 124/70 and normal heart tones. An allergy survey disclosed strikingly positive reactions to several foods, particularly milk and also several inhalants.

Patient was placed on allergic food elimination diet and given antihistaminics to be used as necessary for any mild respiratory flare-ups. He declined inhalant desensitization.

His subsequent course has been exceedingly gratifying, except for one attack of paroxysmal tachycardia which occurred following a banquet when he attempted several allergenic foods. Otherwise he has been free of both the extrasystoles and paroxysmal tachycardias. Any increased nervous strain is now more easily controlled by mild sedation. He feels more at ease and less irritable generally, and having a highly developed, inquiring, scientific mind, he wonders why foods had not previously been considered. Incidentally, the one attack of paroxysmal tachycardia for which there was the occasion to treat him, responded most quickly by the addition of castor oil for yielding a more complete and prompt bowel catharsis. Previous attacks frequently required two to three days of complete bed rest and the usual cardiac medications and sedatives (Fig. 2).

Case 3.—Mr. F. H., aged sixty-nine, was admitted to hospital in a semi-comatose state with acute pulmonary edema, pulse rapid and markedly irregular, blood pressure 160/90, heart sounds distant and of poor quality. Patient responded to the

usual cardiac emergency management after a stormy eight-hour period. The next day his condition improved sufficiently to elicit the history of nocturnal dyspnea of several years' duration, worse in the past two months. He had eaten fried chicken and fried potatoes for the first time in years the evening of the attack. He awakened at 1:00 a.m. with marked abdominal distention and rapidly progressive shortness of breath.

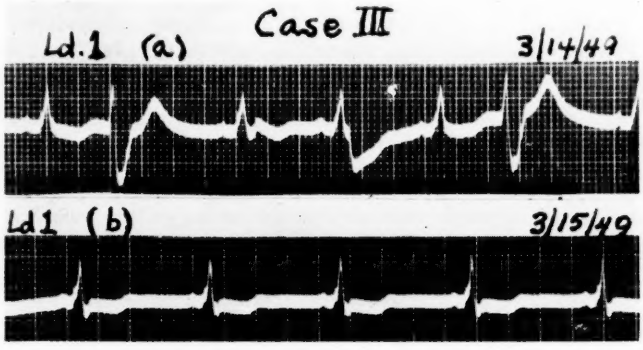

Fig. 3. Case 3. (a) Multiple ventricular extrasystoles. (b) Regular sinus rhythm; digitalis effect.

Further history revealed allergic family background: mother had colitis, and father had asthma. Patient himself had frank asthma at sixteen years of age, with hives, definite food idiosyncrasies to milk, citrus, tomatoes, fried foods and eggs. Proximity to chicken-coop always made his chest tighten up. Skin tests revealed positive reactions to cotton seed oil, citrus, chicken feathers, dust and ragweed.

He was put on allergy exclusion diet and his feather pillow removed. Maintenance doses of digitalis and aminophylline were continued. Within one week the patient felt better than he had in years; lungs were clear; heart sounds were of slightly better quality; there were no extrasystoles and the blood pressure was 100/70; digestion was much improved. He made the trip back North by auto and feels fine. Electrocardiogram taken one and one-half days after attack still showed numerous extrasystoles. Two days later there were no extrasystoles; digitalis effect was noted but no evidence of coronary occlusion (Fig. 3).

Case 4.—Mrs. E. I., aged forty-eight, with known rheumatic heart disease of two years' duration was referred by a cardiologist in her previous residential city. She had a double mitral lesion and aortic insufficiency with auricular fibrillation, and had been in chronic decompensation for at least two years, moderately well helped by salt-poor diet, digitalis and diuretics.

On allergic inquiry it was noted that the patient developed hives from tomatoes and strawberries; citrus and walnuts produced canker sores; milk caused gaseous distention and constipation.

In addition to the cardiac regime, patient was placed on an allergy exclusion diet and antihistaminics when indicated. On this program she felt much improved and for the first time in two years was able to do without an intravenous mercurial injection for five months. At this time she reappeared at the office with the history that she had done well until Christmas when her heart became more rapid without change in digitalis dosage. She developed severe gaseous distention and the chest

was becoming increasingly congested. Further inquiry revealed that on the day of the onset of the new discomfort patient broke her allergy diet and ate peanuts, chocolate ice cream and cake. She was given castor oil as a laxative, and digitalis dosage temporarily increased. Within two days patient felt fine; pulse rate slowed thirty beats, resuming her usual rate of 68 to 80 per minute.

Case 5.—Mrs. M. P., aged fifty-one, with chronic rheumatic heart disease, had been in decompensation for two years, poorly controlled by the usual cardiac measures, e.g., digitalis, diuretics and salt-poor diet. Further inquiry revealed an allergic family background. Patient also complained of frequent sinus headaches, sneezing spells, constipation, gaseous distention and several known food intolerances.

With the help of food diaries, several skin tests and pulse rate correlations, the patient was able to eliminate several food offenders which had produced headaches, tightening and gaseous distention in the epigastrium. She noted also that several foods increased the heart rate. On the exclusion of the suspected foods the patient had done very well, and the tendency to "breaks" in her heart compensation has been minimized. Recently she returned to the office complaining of daily headaches of one week's duration that were very disturbing to her physical and mental balance. Inquiry revealed no significant change in diet. In view of the fact that the oak pollen season was then at its height, she was tested for oak with other controls. A markedly positive test was obtained, and patient obtained quick relief with antihistaminics, and once again she was spared a possible episode of cardiac decompensation.

Case 6.—T. T., a six and one-half-year-old boy, had recently moved to Florida from Pittsburgh, Pa., on advice of his physician, because of a moderately severe attack of acute rheumatic fever for which he had been hospitalized the previous winter, and the history of frequent upper respiratory infections.

The mother complained that in spite of change of climate the child still had frequent respiratory flare-ups with blocked nose, sore throat and transient swelling and pain in the joints. He had continued to be very nervous, restless, with twitching of fine muscles and an eye tic. Physical examination revealed a fairly well built six-year-old boy, appearing restless and nervous. Nasal turbinates were markedly congested and edematous; uvula was elongated and swollen; pharyngeal wall was slightly reddened with small lymphoid follicles that appeared turgid. Heart revealed no enlargement; a sinus arrhythmia with tachycardia 120 per minute and a definite systolic murmur heard throughout the precordium. Electrocardiogram and blood count were normal, sedimentation rate slightly elevated. It was felt that there were many allergic features present in this case. Allergy survey revealed positive reactions to grass, chicken feathers, house dust, oak, and several foods. He received hyposensitization treatments for the inhalants, and an allergy elimination diet, with excellent results. Six months later he was completely asymptomatic, with normal heart findings, marked improvement of personality and absence of nervous irritability.

Case 7.—A thirty-four-year-old dentist had precordial discomfort amounting to slight heaviness, short of frank pain. A year before he had had a similar experience. He was seen at night because of his feared heart attack. Examination revealed a well-developed male not acutely ill; pulse, blood pressure and cardiac findings were normal. The nasal mucus membranes were turgid, and the breath sounds over the left main bronchus were somewhat harsher than the right. Inquiry revealed that there was a hay-fever history, and that both precordial episodes occurred during the season of grass pollination. An antihistaminic was given and on the following day suspicions of pollinosis were confirmed by brilliantly positive skin tests. The electrocardiogram was entirely normal. The symptoms are due to allergic bronchial ir-

ritation and spasm, probably resulting in a mild subasthmatic bronchoconstriction with referred pain. Had it been on the right side the physician would not have been called.

Case 8.—A sixty-eight-year-old merchant had complained of loss of appetite and shortness of breath in May. There had been recent noticeable sneezing. He feared heart disease because of shortness of breath the previous August following a Turkish bath, at which time he was told to see a heart specialist. Electrocardiogram was normal at that time and the repeat in May showed no change. He was found positive to grass, ragweed and oak pollens on earlier skin tests. Removal of milk from diet reduced intestinal gas formation. Symptomatic treatment yielded a completely successful outcome and patient one year later has remained free of any so-called cardiac complaint.

Case 9.—A fifty-four-year-old housewife had cough and choking spells for seven years, worse in spring. The year before she was referred by her physician to a heart specialist who proclaimed her normal and offered no therapeutic suggestions. Her mother had also "choked-up," and a sister had frank asthma. The patient could not eat greasy foods and had several food intolerances. Bronchoscopic examination, electrocardiogram, chest x-rays and gastrointestinal series were normal. Skin tests for pollens and a few foods were positive. Early attempts at hyposensitization increased symptoms. Later events proved that the skin was hyposensitive and the patient hyperreactive.

Specific as well as adjunctive therapy has yielded satisfactory results, save for some return of symptoms during sudden seasonal increases in pollen and mold counts.

COMMENT

The evidence cited above is *not* applicable to the *majority* of cases in any one category. It offers nothing new or radical in clinical allergy. It is felt, however, that allergically oriented physicians can do more for many of the so-called cardiac invalids than is offered in routine medical care. Indeed, several pitfalls of diagnosis and therapy may be avoided. In accomplishing this a great weight may be lifted from an otherwise (and unnecessarily), disturbed patient and family, which may at the same time be spared social and economic dislocations of major proportions.

In the development of medicine we have now arrived at the stage where the accurate evaluation of clinical therapeutic results is too frequently said to be invalidated by variable effects on the patient of the personality of the practitioner. Psychogenic factors present in the patient are likewise alleged to detract from the soundness of any definitive conclusions. No doubt both must be borne in mind. However, it is well-nigh impossible to carry into the clinic the rigid controls usually attainable and even mandatory in the laboratory investigation of experimental animals. It simply cannot be done. One must perforce rely on the all too lax and flexible criteria of subjective and objective benefit to the patient, which, fraught as it is with all kinds of error, is after all the ultimate measure of successful clinical therapy.

SUMMARY AND CONCLUSIONS

1. A group of cases presenting complaints of cardiac origin or implication has been studied. A small but definite proportion of these has been found either on history or physical examination to show evidences of allergy.

2. Such patients when managed allergically may gain prompt dramatic and at times lasting relief from their disabilities. The allergy may be, with rare exceptions, but a contributory cause to the breakdown of an already overburdened individual. This additional therapeutic endeavor is often gratifyingly rewarded.

3. This group may constitute but a small proportion of all cases in these general clinical categories. However, the importance of a possible improvement in the social and economic outlook for these individuals must be constantly borne in mind.

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HAY FEVER IN PALESTINE
Second Report

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SINCE the appearance of the "First Report on Hay Fever in Palestine"[4] in 1941, the accumulation of several new facts and experiences indicated the publication of a second report, broadening and rectifying the original thesis. The main correction involves the recognition of the occurrence of hay-fever reactions not only during the spring, as was originally stated, but also during the autumnal season, and in rare cases during the entire year. In describing these changes and new observations, the order of the original paper will be followed.

GEOGRAPHIC AND CLIMATIC CONDITIONS

Although quite naturally the actual climatic conditions of the country have not changed during this short period, the blossoming time of several plants, especially in Jerusalem, has been considerably increased. This has been caused by an improvement in the irrigation and watering facilities. In Jerusalem, for instance, the construction of a water pipeline has led to a longer blossoming season year by year. In the country at large, the increase of land cultivation and the completion of more extensive artificial watering systems, has had the same effect. Then too, this has contributed to the growth of additional and more abundant grasses, shrubs and trees. Originally the heavy khamsins (sirocco) in April and May, with their desiccating easterly winds, had often been enough to end the blossoming season and to dry up the small grasses (relative humidity sometimes decreases almost to zero; values of 5 to 10 per cent are not rare). Now, however, such grasses, through artificial watering, have had their pollinating season extended and intensified. Plants which were formerly considered as rare causes of hay fever now have a much longer season and are of increasing significance. The four to six weeks difference in the blossoming time throughout the country is a result of the wide range of climatic conditions natural in a country which, within a very small area, includes most of the known geographical formations. The spring season blossoming times are approximately as follows:

1. The Jordan Valley from the end of February until the end of March, in watered places until the middle of April.

2. The coastal plain and Esdraelon from the beginning of March until the end of April or from six to seven weeks. Some cases of hay fever are seen until the middle of May, caused mostly by the pollen of Bermuda grass.

I am much indebted to Dr. M. Zohary and Dr. N. Feinbrun of the Department of Botany, Hebrew University, Jerusalem, for their helpful assistance with botanical suggestions and classifications.

3. The rest of the country, the hill region, from the end of March until the middle or end of May, and sometimes until the middle of June, or from seven to eight weeks or more.

The Haifa Bay, its surroundings and the coastal plain in general have a fall season in September and October. There are many cases of rhinitis and asthma which occur during this period, the causes of which were not clear before the recognition of the autumnal season. This question will be discussed later.

THE CHIEF HAY-FEVER PLANTS OF PALESTINE

In addition to the twenty-two wind-pollinating "plants with practical significance" and the nine non-wind-pollinating "which are deserving of special mention, owing to some particular individual importance," of the first report, we can now list forty-five plants (thirty-three wind-pollinating and twelve non-wind-pollinating).

That these plants do cause hay fever has been verified by direct exposure, positive skin reactions with the pollen extract and successful treatment with pollen extract. Excluded are only *Pinus halepensis* and *Ceratonia siliqua,* since patients gave no response to extracts of their pollen.

HAY-FEVER PLANTS OF PALESTINE*

1. *Acacia farnesiana* (Leguminosae), n, IV-XII. Pollen very toxic for those allergic to it; but since it is not anemophilous, only few are affected.

2. *Agropyron junceum,* Couch grass, coastal plain (Gramineae), IV-V.

3. *Ailanthus glandulosa,* Paradise tree (Simarubaceae), n, IV-V. Cultivated, tree grows rapidly; in recent years, very common here.[1]

4. *Amaranthus graecizans,* Tumble weed; *Amaranthus retroflexus,* Redroot pigweed (Amaranthaceae), VI-X. Careless weeds, they shed relatively little pollen.

5. *Ambrosia maritima* (Compositae), V-XI. An exotic species of ragweed, on the coastal plain. Up to the present there has been only one case of hay fever recorded against it. "Even Americans living here who were sensitive to the American ragweeds remain unaffected by the weed."[4]

6. *Andropogon halepensis* (Gramineae), V-XII. Occurs as a weed on irrigated lands throughout the country. *Andropogon hirtus* on rocky ground.

7. *Avena sterilis,* oat (Gramineae) and Avena barbata, III-V.

8. *Calycotoma villosa* (Leguminosae), n, II-IV. Occurring especially in the hills.

9. *Casuarina torulosa* and *tenuissima* (Casuarinaceae), VIII-X. Cultivated.

10. *Ceratonia siliqua,* Locust tree or carobtree, St. John's tree, (Leguminosae), n, VIII-XI. General except on higher and cold hills, is alleged to cause hay fever. Patients claim definitely to suffer from sneezing and a nasal discharge when near the plant, especially because of its penetrating odor. Considerations similar to those put forward in connection with citrus blossoms apply here with the difference that citrus odor is quite pleasant. We were unable to obtain positive skin reactions with extracts of this pollen.

11. *Chenopodium murale* (Chenopodiaceae), III-XII. Is present almost throughout the year.

*The months of the blossoming times are designated by the Roman numerals I-XII (January is I, and so forth). All non-wind-pollinating plants are followed by an "n."

POLLINATION CALENDAR (PALESTINE)

	Jan. I	Feb. II	Mch. III	Apr. IV	May V	June VI	July VII	Aug. VIII	Sept. IX	Oct. X	Nov. XI	Dec. XII
1. Acacia farnesiana				X	X	X	X	X	X	X	X	X
2. Agropyron junceum				X	X							
3. Ailanthus glandulosa				X	X							
4. Amaranthus spp.*						X	X	X	X	X		
5. Ambrosia maritima					X	X	X	X	X	X	X	
6. Andropogon halepensis					X	X	X	X	X	X	X	X
7. Avena spp.*			X	X	X							
8. Calycotoma villosa		X	X	X								
9. Casuarina spp.*								X	X	X		
10. Ceratonia siliqua								X	X	X	X	
11. Chenopodium spp.*			X	X	X	X	X	X	X	X	X	X
12. Citrus spp.*			X	X								
13. Cynodon dactylon			X	X	X	X	X	X	X	X		
14. Cyperus papyrus					X	X	X	X	X	X		
15. Echinochloa colonum				X	X	X	X	X	X	X	X	X
16. Eragrostis cynosuroides							X	X	X	X		
17. Eucalyptus	X								X	X	X	X
18. Hordeum spp.*		X	X	X	X							
19. Imperata cylindrica			X	X	X	X						
20. Inula viscosa							X	X	X	X	X	X
21. Juncus acutus				X	X	X						
22. Koeleria phleoides			X	X								
23. Mercurialis annua	X	X	X	X								
24. Olea europaea					X							
25. Panicum repens	X			X	X	X	X	X	X	X	X	X
26. Phleum spp.*			X	X								
27. Phragmites communis							X	X	X	X	X	X
28. Pinus halepensis			X	X								
29. Plantago psyllium			X	X								
30. Poa spp.*	X	X	X	X	X	X						X
31. Polypogon monspeliensis			X	X								
32. Ricinus communis			X	X	X	X	X	X	X			
33. Robinia pseudoacacia				X	X							
34. Saccharum aegyptiacum	X							X	X	X	X	X
35. Salicornia herbacea								X	X			
36. Scirpus litoralis					X	X	X	X	X	X		
37. Sorghum annuum						X	X					
38. Triticum			X	X	X							
39. Urtica spp.*		X	X	X								
40. Zea mays						X	X	X	X			
41. Tilia						X	X					
42. Jasminum				X	X	X	X	X				
43. Syringa vulgaris				X	X							
44. Salsola kali				X	X							
45. Morus nigra			X	X								

*For the species involved see the list of hay-fever plants.

12. *Citrus aurantium,* orange and grapefruit. *Citrus limonum* and dulcisa, lemon. *Citrus mandarensis. Citrus nobilis,* n, III-IV.

Hay fever caused by citrus pollen is rare and occurs only with people working in citrus groves or in their vicinity.[4] Many people who believe they suffer from citrus blossoms are allergic to Cynodon dactylon and other grasses growing in the groves.

13. *Cynodon dactylon,* Bermuda grass, yablith (Hebrew name) or indgil (Arabic), (Gramineae), III-X. Is still the most important cause of hay fever in the country.[4]

14. *Cyperus papyrus* (Cyperaceae), V-X. *Cyperus longus.*

15. *Echinochloa (Panicum) colonum,* purple panic grass, IV-XII.

16. *Eragrostis cynosuroides* (Gramineae), VII-X. Summer blossoming plant, occurs only in the coastal plain from Acre southward.

17. *Eucalyptus rostrata* (Myrtaceae), n, IX-I. Blooming chiefly in the coastal plain.

18. *Hordeum murinum,* barley grass (Gramineae), II-V. *Hordeum vulgare.*

19. *Imperata cylindrica* (Gramineae), III-VI. On the coastal plain and in the upper Jordan Valley.

20. *Inula viscosa* (Compositae), n, VII-XII. In marshes and swampy soil, in the hills. The smell of the leaves is very irritating.

21. *Juncus acutus* (Juncaceae) Great sea-rush, IV-VI.

22. *Koeleria phleoides* (Gramineae), III-IV. Throughout the country, including the desert.

23. *Mercurialis annua,* Mercury plant (Euphoriacea), I-IV. Is spread throughout the country, but not very profusely.

24. *Olea europaea,* Olive, (Oleaceae), n, V. Although it is not wind-pollinating, the pollen is light enough and causes hay fever.

25. *Panicum repens* (Gramineae), IV-I.

26. *Phleum subulatum* (Gramineae), Cat-tail grass, III-IV. *Phleum arenarium (Phleum pratense,* Timothy grass does not occur here.)

27. *Phragmites communis* (Gramineae), Common reed, VII-XII.

28. *Pinus halepensis,* Aleppo pine, III-IV. Produces masses of pollen, which seldom cause hay fever.[2,9]

29. *Plantago psyllium,* plantain (Plantaginaceae), III-IV.

30. *Poa annua,* low spear grass (Gramineae), XII-VI. Grows in irrigated places. Poa bulbosa, meadow grass III-IV, Poa Heckeli III-IV (Poa pratensis does not grow here.)

31. *Polypogon monspeliensis,* Annual beard grass (Gramineae), III-IV. Especially in damp places.

32. *Ricinus communis.* Castor oil plant (Euphorbiaceae), III-IX. It grows chiefly on the coastal plain where it is widespread. Especially III-V.

33. *Robina pseudacacia* (Leguminosae), n, end of IV-V. Widespread.

34. *Saccharum aegyptiacum* (Gramineae), VIII-I.

35. *Salicornia herbacea,* glasswort (Chenopodiaceae), VIII-XI. In salt places, common.

36. *Scirpus litoralis* (Cyperaceae), V-X.

37. *Sorghum annuum* "durrha" (Gramineae), summer VI-VII. Is domestically cultivated, but only in Arab localities. *Sorghum vulgare,* the chimney millet, "Durrha," is a common weed in Africa.

38. *Triticum vulgare,* wheat cereal (Gramineae), III-V. Triticum durum is grown throughout the country.

39. *Urtica urens,* small nettle (Urticacae), II-IV. *Urtica pilulifera,* Roman nettle.

40. *Zea mays,* corn (Gramineae) summer months, VI-IX (- X). Without great significance because of the high weight of its pollen.

Occasionally we see a patient with hay fever symptoms derived from:

41. *Tilia,* n, VI-VII.

42. *Jasminum,* n, IV-VIII.

43. *Syringa vulgaris,* lilac, n, IV-V.

44. *Salsola kali,* Russian thistle, IV-V. Coastal plain.

45. *Morus nigra,* black mulberry, III-IV.[3]

As already mentioned, we observed an additional hay-fever season in autumn in some parts of Palestine. The plants responsible for this hay fever are the following:

Amaranthus graecizans	Cynodon dactylon	Panicum
Amaranthus retroflexus	Cyperus	Phragmites communis
Casaurina ceal	Eragrostis	Saccharum
Ceratonia siliqua, n	Eucalyptus	Salicornia
Chenopodium	Inula viscosa, n	Scirpus
		Zea mays

DISTRIBUTION OF POLLEN-ALLERGY AND ITS CLINICAL SIGNIFICANCE

Although it is impossible to give the exact number of patients, the percentage of hay-fever sufferers in Palestine is approximately the same

as in Europe, but is smaller than in North America. This number, however, is considerably greater than is generally assumed by physicians and patients alike. The reason for this is that many cases are not recognized as such and certainly not when they later develop asthma. During the course of systematic allergy testing of asthma patients during summer and autumn, a large number were found sensitive to pollen extracts prepared from the country's pollen. Immediate desensitization brought about quick relief from asthma and, following pre-seasonal or coseasonal treatment with pollen extracts, the asthmatic condition did not recur in the following years as before this treatment.

THERAPEUTIC NOTES

Since 1929,[5] we have been using intracutaneous injections of pollen extracts prepared in accordance with individual susceptibility. It was observed that the intracutaneous treatment requires more injections than the subcutaneous method, and no unpleasant side effects were observed with the intracutaneous treatment.

Good results were obtained with both the perennial and the pre-seasonal treatment. Even after the beginning of the hay-fever season these injections had a surprisingly beneficial effect.[6,7]

The result of the treatment depends largely on the use of extracts prepared for each patient according to his special allergy to the various pollens. We are not able to confirm the opinion that different kinds of pollen are so related to each other that it makes no difference which are to be used for injections, for example, that the use of fiorin (timothy) extract alone would be sufficient for a successful treatment for hay fever due to grasses (Harley).[8] Even if the patient proves allergic to timothy, treatment with it alone is not sufficient if he is allergic to other plants at the same time. These questions shall be discussed in detail in another report.

SUMMARY

The following can be stated as a supplement to the "First Report on Hay Fever in Palestine" (1941):

1. The blossoming periods are longer than previously reported, following the substantial increase in the area of cultivated and irrigated land during recent years, and in Jerusalem following the construction of a new water supply system.

2. In addition to the spring hay fever during March, May, and June, there also occurs an autumnal hay fever during September and October in some parts of the country (coastal plain). Isolated cases have been known to occur practically through the entire year.

3. New hay-fever plants for Palestine are reported, including some effective during the autumn season.

(Continued on Page 381)

THE USE OF A COMBINATION OF TWO ANTIHISTAMINIC DRUGS IN THE TREATMENT OF ALLERGIC VASOMOTOR RHINITIS

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THEPHORIN* (2-methyl-9 phenyl-2, 3, 4, 9-tetrahydro-1-pyridindene hydrogen tartrate) has been shown to differ from the other known antihistaminic compounds in its side effects on humans.[1,3,4] In contrast to the other antihistaminics, which most commonly produce depression and somnolence, Thephorin has as its most common side reactions stimulation and insomnia.

It seemed possible to combine this drug with one of the other antihistaminics, providing an antagonistic or nullifying effect on the side reactions and securing an additive antihistaminic effect. The drugs used in this investigation were Thephorin and Trimeton** (phenyl (2-pyridyl) (β-N,N-dimethylaminoethyl) methane hydrochloride).

EXPERIMENTAL

Two hundred patients, each having symptomatic vasomotor rhinitis due to ragweed sensitivity, were the subjects for this investigation. The patients were given each of the two drugs separately in doses of 100 mg. per day, and the two drugs together in a total dosage of 200 mg. per day. Each patient received each form of medication for a period of one to three weeks during the 1948 ragweed season. The patients were divided into three equal groups, and each group received the drugs in different sequence in order that none of the groups would be taking the same drug at the same time. This was done to compensate for the changing pollen count and seasonal variation in symptoms.

The patients were seen at least once a week and questioned concerning the effectiveness of the drug in controlling symptoms. If the patients volunteered any information concerning side reactions, as was usually the case if side reactions were present, they were recorded. If the patients did not volunteer information about side reactions, they were questioned briefly for the presence of untoward effects. The grading of the degree of symptomatic relief and severity of side reactions was made as follows:

Degree of symptomatic relief: O, no relief; +, slight, up to 50 per cent relief of symptoms; ++, moderate, from 50 to 90 per cent relief of symptoms; +++, complete relief of symptoms.

Side reactions: O, none; +, mild, or elicitable only on questioning; ++, moderate, of sufficient degree to be annoying, and volunteered by

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*Thephorin, brand of Phenindamine, was supplied through the courtesy of Hoffmann-LaRoche, Inc., Nutley, New Jersey.

**Trimeton, brand of Prophenpyramine, was supplied through the courtesy of Schering Corporation, Bloomfield, New Jersey.

TABLE I. RESULTS OF TREATMENT OF 200 HAYFEVER CASES WITH THEPHORIN; TRIMETON, AND THEPHORIN COMBINED WITH TRIMETON

	Thephorin	Trimeton	Thephorin + Trimeton
Total number of patients getting symptomatic relief from drug	177	175	189
Degree of relief (number of patients):			
+ (slight)	65	62	31
++ (moderate)	90	94	119
+++ (complete)	22	19	39
Total number of patients having side reactions	85	48	86
Severity of reactions (number of patients):			
+ (mild)	53	36	56
++ (moderate)	11	8	26
+++ (severe)	21	4	4

patient without questioning; +++, severe, of such a degree as to require discontinuation of the medication.

At the conclusion of the study the patients were asked to designate the type medication which they preferred and to compare these drugs with other antihistaminics which they had taken previously.

RESULTS

In Table I is listed the number of patients receiving benefit from the two drugs and the combination, and the number of side reactions observed with each.

The number of patients getting relief from the combination of the drugs was significantly greater ($P=<.02$)† than that observed for either of the two drugs administered separately. There was also a significantly greater degree of moderate and complete relief obtained from the combination ($P=<.001$). There was no significant difference in the number of side reactions observed with Thephorin alone and the combination. However, the Thephorin had to be discontinued in twenty-one patients, while only four patients required discontinuation of the combination or the Trimeton. The number of side reactions observed with Trimeton was significantly smaller than that obtained with the other two forms of treatment ($P=<.002$).

Table II shows the frequency distribution of the types of side reactions to the several forms of medication.

There were fifty patients in the group who reacted to Thephorin with excitatory phenomena on doses of 100 mg. per day. When these patients received this dose combined with an equivalent dose of Trimeton, only twenty-one of the fifty patients complained of side reactions ($P=.001$). Of these, ten still complained of nervousness and excitation; ten complained of dizziness, and one complained of constipation. There were seventeen of the 200 patients who reacted with depression and somnolence to Trimeton on doses of 100 mg. per day. When an equivalent amount of

†The data was analyzed by the method of x^2. P is the percentage probability of the observed differences occurring by chance; $P = .05$ or less is considered significant.

TABLE II. TYPE AND FREQUENCY OF SIDE REACTIONS OBSERVED WITH THEPHORIN, TRIMETON, AND THEPHORIN COMBINED WITH TRIMETON

	Nausea	Anorexia	Constipation	Abdominal Pain	Dizziness	Nervousness, Jitteriness, Exhilaration	Insomnia	Drowsiness, Depression	Fever, Flush	Palpitation, Tachycardia	Dryness of Skin	Dryness of Mouth	Headache	Syncope
Thephorin (Number of patients having reactions)	24	7	4	4	9	24	37	7	7	4	4	4	2	0
Trimeton (Number of patients having reactions)	7	0	0	0	22	10	0	17	0	0	2	5	0	0
Thephorin + Trimeton (Number of patients having reactions)	21	2	4	2	30	11	9	30	4	2	4	13	4	1

Thephorin was administered simultaneously, eleven of these patients complained of side reactions ($P=.01$); seven complained of depression and four complained of dizziness.

From the above two groups there were nine patients who exhibited both a reaction of excitation to Thephorin and a reaction of depression to Trimeton. When the two drugs were given in combination to these patients, all still exhibited side reactions to the medication. Six stated that they were depressed, and three stated that they felt dizzy or intoxicated.

On questioning at the end of the experiment seventy-five of the patients preferred the combination, sixty preferred Trimeton, fifty preferred Thephorin, and fifteen of the patients felt that all were of about equal effectiveness.

One hundred and ten of the 200 patients had also previously taken both Benedryl and Pyribenzamine. Of these patients, 71.5 per cent found one of these three forms of medication superior to either Benadryl or Pyribenzamine; 28.5 per cent found either Benadryl or Pyribenzamine superior to any of the drugs used in the present study.

DISCUSSION

We have evidence that the combination of the two drugs afforded a greater degree of symptomatic relief than either of the two drugs taken separately, although an effect as good might have been derived from doubling the dose of either of these drugs. However, there is good evidence from the work of others that the incidence of side reactions tends to increase in proportion to the size of the dose of either of these drugs.[1-4] Thus, by doubling the dose of either drug we would expect to double the incidence of side reactions. The observed total incidence of side reactions to the combination was not significantly different from that observed with Thephorin, but the incidence of severe reactions was significantly smaller with the combination. Although the incidence of side reactions with the combination was greater than that observed with Trimeton alone, the number of severe reactions observed was the same. Thus, there was antagonism

in the side reactions of the two drugs, although this antagonism was not complete.

The total dose in the combination was double that of the drugs given separately, which may have given rise to other toxic symptoms beyond the mild stimulation or depression noted at a lower dose range. A better effect might have been observed if we had attempted to balance the dosage of the two drugs in proportion to the magnitude of the stimulation or depression effects of each drug on the individual patient.

SUMMARY AND CONCLUSIONS

Data are presented on the administration of Thephorin, Trimeton, and the two drugs in combination for a period of from one to three weeks each, to 200 patients with allergic vasomotor rhinitis due to ragweed.

The incidence and degree of symptomatic relief was significantly greater with the combined drugs than with either of the drugs administered separately. The incidence of side reactions with the combined drugs was the same as that observed with Thephorin, but greater than that observed with Trimeton, although the number of severe reactions observed with the combination was no greater than observed with Trimeton, and significantly less than observed with Thephorin. Of the patients, 37.5 per cent preferred the combination, 30 per cent preferred Trimeton, 25 per cent preferred Thephorin, and 7.5 per cent found them all of about equal usefulness. It is concluded that there was a definite, though incomplete, antagonism in the side reactions of the two drugs.

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PSYCHOTHERAPY COURSE FOR ALLERGISTS

Dr. Sandor Rado, Clinical Professor of Psychiatry and Director of the Psychoanalytic Clinic for Training and Research, Columbia University, in co-operation with The American College of Allergists, is presenting a Psychotherapy Course for Allergists in New York City. Lectures will be held 9:00 a.m. to 12:30 p.m. and 2:00 p.m. to 5:00 p.m. daily, November 6 through November 10, 1950. Registration fee is $100. Information is obtainable from Dr. H. A. Abramson, 133 East 58th Street, New York, N. Y.

INHIBITION OF RED CELLS ISOAGGLUTINATION BY ALLERGENIC EXTRACTS—PRELIMINARY REPORT

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THE house dust antigen prepared according to a method developed by Sutherland[3] has the property of inhibiting the isoagglutination of human erythrocytes, as demonstrated by Rimington, Stillwell and Maunsell.[2]

I found that this property is not restricted to the dust antigen but is common to many other extracts obtained by a similar procedure, all of which exhibit a great biological activity in scratch or intradermal tests.

As no method is available to determine *in vitro* the allergen content of the extracts, it is obvious that this test would be a very convenient one if the inhibitory power is due to the antigen. Up to the present no definite proof of this has been obtained; however, I have found a very close correspondence between the titer of inhibition and the biological activity, and in any case the increase or loss of one of such properties produces a corresponding modification of the other.

EXPERIMENTAL

Preparation of Extracts.—The material is extracted during forty-eight hours in N/100 ammonia. It is not previously defatted except in the case of seeds. The resulting fluid is clarified by paper filtration, sodium benzoate is added (20 gm. per liter) and then HCl 1:5 until blue to Congo red. The precipitate of benzoic acid, that adsorbs the antigenic fraction, is filtered through paper in a Buchner, and dissolved in acetone where the antigen remains insoluble. It is washed with acetone, alcohol and ether. The greyish or brownish powder obtained is dissolved in a mortar in NaOH N/10, then adjusted to pH 7.5 with HCl N/1 and centrifuged. The insoluble is discarded. The dilution used varied between 0.5 and 5 per cent of solids according to the potency of the corresponding material.

The yield of solid "crude antigen" varies widely with different extracts. Approximately the following results were obtained:

0.015 to 0.05%	cow, cat and dog hair; chicken and turkey feathers; jute; house dust; tufts of the seeds of Platanus acerifolia (buttonwood).
0.05 to 0.15%	horse and goat hair; hemp; orris root; tufts of the seeds of Chorisia sp.
0.15 to 0.60%	rabbit hair; goose and duck feathers; sheep wool; linseed; flax; pyrethrum; tobacco; alfalfa hay.
0.60 to 1.2%	cottonseed; silk worm; dust of grain mill.

As a rule scratch tests were used and the extracts were maintained in the cooler without sterilization. When used for intradermal tests they were diluted 1:1000 and sterilized by Seitz filtration. In a few cases where sterilization has been carried out by heating at 100° C. during thirty minutes, no significant loss of activity was observed.

Dr. Binaghi is Chief of the Laboratories of the National Institute of Allergic Diseases.

Determination of the Inhibition of Isoagglutination.—One part in volume of the antigen is added to all the tubes of a series containing one part of a suspension of washed red cells (approximately 1:20 in saline), and three parts of saline. To each tube is added five parts of agglutinating sera conveniently diluted, the dilution corresponding to a tube being twice that of the previous one. A parallel control series is made without antigen and with four parts of saline. A, B or AB group erythrocytes can be used.

Tubes are incubated fifteen minutes at 37° C., then centrifuged one minute at 1500 r.p.m., readings being made after not less than fifteen minutes at room temperature, shaking the tubes immediately before observation. The end point is microscopically read. I consider plus-minus agglutination when very few clumps of two to four cells are present, and plus agglutination when there are clumps of more cells. Moving the stage of the microscope and producing a little sliding of the drop, decision can be made between agglutinated and simple contacting cells.

No differences are observed between first incubating the sera and the antigen and then adding the cells, or incubating the cells and the antigen and then adding the agglutinating sera.

DISCUSSION

All the extracts prepared showed appreciable inhibitory activity, diminishing the agglutinating titer of the sera from two to sixteen times in the conditions described. The biological activity was also very high.

The inhibition test is less sensitive than the biological one: extracts that possess a demonstrable inhibitory power can be diluted about ten times and yet be very adequate for scratch testing. In this connection the technique of Sutherland is specially useful since it is very simple and rapid and produces extracts of very high concentration with the additional advantage of getting solids that remain practically unaltered with time.

The house dust antigen described by Boatner and Efron[1] presents equally high inhibitory power.

No experiences have been realized with pollen extracts.

SUMMARY

1. It is demonstrated that allergenic extracts possess the property of inhibiting red cells isoagglutination.

2. In all the cases studied there is a close correspondence between this inhibitory property and the biological activity.

3. It is suggested the possibility of using such test as a method of estimating *in vitro* the potency of allergenic extracts.

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THE TREATMENT OF ACUTE POISON IVY DERMATITIS WITH 3-n-PENTADECYL CATECHOL BY THE INTRADERMAL ROUTE

A Preliminary Report

HARRY KEIL, M.D.
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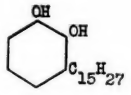
THE treatment of poison ivy dermatitis resolves itself into two separate problems: first, the prevention of attacks on exposure to the plant; second, the alleviation of the acute attack. This communication is concerned only with the latter phase. The treatment of acute poison ivy dermatitis with plant extracts has been vigorously criticized by Stevens[5] and, more recently, by Howell.[3] These criticisms have emphasized the following points: the variability in the potency of samples of poison ivy extract found on the market; the many untoward reactions encountered and the occasional worsening of the attack; and the failure to influence the clinical course as well as the subjective complaints. Howell, for example, found no difference in the results obtained in twenty-three cases of acute poison ivy dermatitis, which were treated with from one to four intramuscular injections of a plant extract, as compared with seventeen instances of acute poison ivy dermatitis, which were treated with nonspecific measures. The average duration of the course in both groups was thirteen days. It must be stressed that the aforementioned criticisms leveled at parenteral treatment of this affection were concerned only with poison ivy extracts, which are admittedly unstable, cannot be quantitatively standardized by chemical methods, and are not free from extraneous plant substances. Moreover, these extracts have been administered by the intramuscular route, less often subcutaneously.

This communication is based on the data derived from the *intradermal* injection of synthetic 3-n-pentadecyl catechol in twenty-seven moderately severe to very severe attacks of poison ivy dermatitis observed in twenty-five patients.* Both the substance used and the method of administration represent a fresh approach to this vexing problem. Although it is difficult at times to assess the value of therapy in this disease, the subjective and objective results obtained in this group of twenty-five severe cases were sufficiently promising to warrant a report at this time.

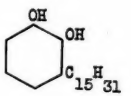
Patch test studies[4] have shown that patients sensitive to the poison ivy plant manifest constant group reactions to a proper concentration of synthetic 3-n-pentadecyl catechol (0.1 to 1.0 per cent in any suitable solvent, for example, isoamyl acetate). The active ingredient in the plant causing this dermatitis is a catechol compound with an unsaturated normal side chain of fifteen carbon atoms in the 3-position, the side chain having an

*Drs. R. L. Parker and A. Neumann independently treated sixteen additional cases of poison ivy dermatitis with this method. At least five were severe examples of the disease. Both expressed satisfaction with the results obtained. Dr. Parker used concurrently one of the alcoholic extracts on the market, and he found that "the results were superior" with 3-n-pentadecyl catechol. I have not incorporated these data here since the cases were not under my own direct observation. These additional data offer a rough comparison and substantiation of the results obtained with the material to be reported in this communication.

average of two double bonds in positions as yet undetermined.[2] On the other hand, synthetic 3-n-pentadecyl catechol differs from the active ingredient in the poison ivy plant in that the side chain is fully saturated. The following formulas will illustrate this difference.



3-n-pentadecadienyl catechol**
(poison ivy "urushiol")



3-n-pentadecyl
catechol

**The same chemical formula designates the active ingredients in rhus diversiloba (poison oak), rhus venenata (poison sumac) and rhus vernicifera (Japanese and Chinese lac tree).

As stated, the active ingredient in the poison ivy plant is an unsaturated oil which is unstable and cannot as yet be standardized by chemical methods. Contrariwise, 3-n-pentadecyl catechol is a crystalline synthetic substance[1] which is potent, can be standardized quantitatively, is stable in oil solution and is easily handled.

Hitherto, most therapeutic endeavors have been based on intramuscular or subcutaneous injections. It was felt that the chances for a more successful method might be increased by placing the injected solution closer to the site of the "shock organ" in rhus dermatitis.

After many preliminary trials with various dilutions,† the most satisfactory concentration for treatment was found to be a dilution of 0.001 per cent 3-n-pentadecyl catechol in sterilized peanut oil. This will be designated as the treatment solution. The dosage of the treatment solution ranged between 0.1 and 0.3 c.c.; the average dose and the optimal one used for the vast majority of cases was 0.2 c.c., which was generally repeated in forty-eight hours. The injection was given into the cutis proper, using a 27-gauge needle, and no attempt was made to raise a wheal. The left arm was injected when the patient was right-handed, and contrariwise, the right arm was used in left-handed people. No other treatment was recommended, and the patients were merely asked to continue, if they wished, any simple bland measure employed prior to observation. In an occasional instance large bullae were drained of fluid when there was mechanical distention in the part.

The side effects encountered with the administration of poison ivy extracts range from local to constitutional exacerbations.[3] In contrast, no disturbing reactions were encountered following the intradermal injection of the treatment solution (3-n-pentadecyl catechol in peanut oil) in the dosage used. In occasional instances the site of injection became slightly indurated and pruritic, especially when the solution was placed superficially enough to produce a wheal, but such effects were mild and transient. Focal reactions in areas of eruption were not encountered, although

†Studies carried out with alcoholic solutions of 3-n-pentadecyl catechol were attempted but had to be interrupted owing to the severe pain experienced by patients.

this is theoretically possible in persons with unusual hypersensitiveness. No constitutional manifestations were seen in this group of patients, nor in the course of other studies, and the medicament was well tolerated by all, including children.

RESULTS OF TREATMENT

The principle of control in evaluating the results of poison ivy treatment is most difficult to carry out with scientific precision. For this reason only moderately severe to very severe cases were intentionally selected for study. Twenty-seven such attacks, occurring in twenty-five patients, were available for analysis. These cases may be divided into two groups (A and B), depending on whether or not patch tests were made prior to treatment.

A.—In the first group (thirteen cases) the patients had rhus dermatitis of a few days' duration. They were patch tested with 3-n-pentadecyl catechol dissolved in isoamyl acetate (testing solution).[5] All were found to be sensitive to the testing solution in either 0.1 per cent or 1.0 per cent or both concentrations. The reading of the tests necessitated a delay of at least forty-eight hours prior to treatment. One of the most striking features following the treatment was the subjective relief of itching, burning or smarting in from two to four days, three days being the average time. The course of the dermatosis in this group was more difficult to evaluate owing to the time element involved. These points are better illustrated in the following case protocols.

Case 1.—A young man had a moderately severe attack of poison ivy dermatitis of a few days' duration. Patch tests with 3-n-pentadecyl catechol gave the following results: 0.1 per cent concentration, a plus-minus reaction in forty-eight hours and a 2-plus reaction in ninety-six hours. He received an intradermal injection of 0.3 c.c. of the treatment solution, with relief of subjective and objective manifestations in three days. Feeling well, he decided, two days later, to clean out the lots adjoining his home. This time he suffered a more severe attack of rhus dermatitis. He was seen two days after the onset of the eruption and immediately received another intradermal injection of 0.3 c.c. of the treatment solution. Again, there was recovery in about three days. In this case, an opportunity was afforded to treat the patient in a second attack, without the delay necessitated by patch testing.

Case 2.—A boy of eight was observed in a moderately severe attack of rhus dermatitis of five days' duration. Patch test with 0.1 per cent 3-n-pentadecyl catechol (in isoamyl acetate) gave a 3-plus reaction in forty-eight hours. He was then given 0.1 c.c. of the treatment solution and was well in two to three days. This may have been the tail end of an attack. However, several months later he returned with a severe attack of poison ivy dermatitis of four days' duration. He was immediately given the same dosage of the treatment solution and this was repeated in forty-eight hours. There was much relief of the severe pruritus in two or three days and the eruption began to fade.

Case 3.—A woman, twenty-seven years old, came in for severe rhus dermatitis confined to the legs. The attack had been present for a few days and the itching was most intense. Patch test with 0.1 per cent 3-n-pentadecyl catechol gave a 2 to 3-plus

reaction in forty-eight hours, which became 3-plus in ninety-six hours. She was given an intradermal injection of 0.2 c.c. of the treatment solution, with marked relief of the itching and the eruption in a few days.

B.—In order to avoid the delay incidental to patch testing, a group of fourteen cases of typical poison ivy dermatitis (including the second attacks in Cases 1 and 2) were treated immediately when first seen. These cases were intentionally selected because they fulfilled two criteria: first, the attack was severe, with no signs of abatement or relief of itching, burning or smarting; second, the patients were observed relatively early in the course, on the average three to four days, in no case beyond the fifth day. This group of patients received two injections (0.2 c.c.), generally at an interval of forty-eight hours. The results obtained were similar to those seen in the first group in so far as the relief of subjective symptoms was concerned. The edematous element present in many cases required about two to three days to subside, and the entire dermatosis faded about the fifth day of observation. These points are illustrated in the following protocols, which are given in greater detail to show that the patients undoubtedly had suffered from rhus dermatitis.

Case 4.—A middle-aged woman had suffered from many severe attacks of poison ivy dermatitis in the past eight years owing to contact with the plant which flourished on her farm in Connecticut. The average duration of poison ivy dermatitis in prior years had been about ten days, and during this period she suffered considerably from itching and burning. She came under my observation on the third day of another, probably the most severe, attack she had yet had. There were multiple, vesiculo-bullous diffuse lesions in the form of patches on the right forearm, both legs and in the right popliteal space. These areas were oozing intensely and required frequent changes of dressings to minimize contamination of the overlying clothes. The itching, which had been intense, was now replaced by pronounced smarting at the sites of ruptured bullae. She received an intradermal injection of 0.2 c.c. of the treatment solution. When she returned two days later, there was considerable relief of the subjective symptoms of smarting and much improvement in the appearance of the lesions. She received another injection and four days later she stated that in the interim the subjective symptoms had been completely relieved. In addition, the eruption had also practically faded. The patient expressed the opinion that the course of her case had been considerably attenuated.

Case 5.—A boy, nine years old, played ball in the country. In order to retrieve balls that went astray, he had to go into the bushes. A few days later he noted an eruption that spread rapidly. He came under observation four days after the onset, with the clinical picture of a most severe attack of poison ivy dermatitis. There was tremendous edema of the face, with vesiculation, and the eyes were completely closed. Extensive diffuse areas of vesicular eruption were present on the forearms, and there were scattered similar lesions on the chest and lower limbs. Pruritus was intense. He was given an intradermal injection of 0.2 c.c. of the treatment solution. When he returned five days later, he not only felt better subjectively but the eruption had faded, except for some dried crusted lesions on the upper limbs. He was given another injection in the same dosage at the request of the mother. A follow-up nine days later revealed that the eruption had disappeared shortly after the second injection.

Case 6.—A man, aged forty-one, chopped down weeds in the country. About four days later, an itchy eruption appeared. He was first seen on the third day after the onset of the dermatosis. At this time he had the clinical appearance of a severe attack of poison ivy dermatitis. There were diffuse patches of vesiculation and linear vesicular lesions widespread over the upper and lower limbs, the trunk and on the face. An intradermal injection of 0.2 c.c. of the treatment solution was given. When seen five days later, there was considerable improvement in the subjective and objective signs of the eruption. Another intradermal injection was given in the same dosage, and two days later the eruption had faded.

DISCUSSION

The principle of using control groups in evaluating the effects of therapy in poison ivy dermatitis is subject to many difficulties. For example, it is almost impossible to select cases of comparable intensity and of equal duration. The inclusion of mild instances of this disease may lead to conclusions of relatively less significance. Under these circumstances it was felt that the second group of fourteen attacks of poison ivy dermatitis of severe type and of extensive distribution provided a valid group for the evaluation of treatment. These cases were seen relatively early in the course; the lesions were widespread, oozed profusely and were often bullous in type; and the pruritus, smarting or burning was intense. This was the sort of attack which would have generally lasted at least ten days to two weeks. Indeed, the past experience of several patients in this group confirmed this duration for previous attacks of comparable severity. The average total duration in this group of fourteen treated cases was eight days from the onset of the attack, with a range of from six to ten days. These results may be roughly compared with those reported by Howell,[3] who recorded the same average duration of thirteen days in a group of twenty-three cases of acute poison ivy dermatitis treated with intramuscular injections of a plant extract and in a group of seventeen cases treated by nonspecific agents. In the absence of specific information, it is assumed that Howell's group of forty cases were average cases of poison ivy dermatitis, and therefore included both mild and severe examples. In contrast, my data are based on selected cases of moderately severe to very severe instances of the disease. Concerning the group of fourteen severe instances (Group B), the results obtained seemed to indicate a shortening of the clinical course by a few days, but the most striking feature was the relatively rapid amelioration in the subjective symptoms of itching, burning or smarting. In short, these severe attacks seemed to be better tolerated by the patients, and the opportunities for secondary complications were reduced owing to diminution in the subjective symptoms. It should be noted, however, that no effect is to be expected in the event of secondary complications, such as pyoderma and the like.

SUMMARY

Twenty-seven moderately severe to very severe attacks of poison ivy dermatitis, observed in twenty-five patients, were selected for treatment

with intradermal injections of 3-n-pentadecyl catechol in peanut oil. The results obtained were especially striking in a subgroup of fourteen very severe attacks of the dermatosis. The outstanding feature was the relatively rapid amelioration of subjective symptoms and the probably shortened course of the eruption. 3-n-pentadecyl catechol, the saturated analogue of the active principle of the poison ivy plant, is a synthetic crystalline substance which is stable in oil solution, can be quantitatively administered and is easily handled. The treatment solution containing 0.001 per cent 3-n-pentadecyl catechol in peanut oil, was injected intradermally in a dosage of 0.2 c.c., which was generally repeated two days later. These injections were painless and given closer to the "shock organ" than has been done hitherto. Constitutional or other important side effects were not encountered. The rationale for the use of this substance in the manner described has been briefly discussed, but the mechanism involved is still under consideration.

ACKNOWLEDGMENT

My thanks are due Prof. C. R. Dawson and Dr. D. Wasserman for the supply of 3-n-pentadecyl catechol, and for their continued interest in this investigation.

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PAPERS FOR SEVENTH ANNUAL SESSION, CHICAGO

Members of The American College of Allergists who intend to submit papers for the Seventh Annual Session are reminded that October 15, 1950, is the deadline. Papers are to be submitted in duplicate, accompanied by an abstract of about 250 words, to the Chairman of the Program Committee, Dr. Albert V. Stoesser, 1409 Willow Street, Loring Park, Minneapolis, Minnesota.

A CYTO-HISTOLOGICAL METHOD AS A DIAGNOSTIC AID IN ALLERGIC ANTRAL SINUSITIS

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THERE is a generally growing comprehension of the importance of early recognition of allergic manifestations in the nose and throat. It is desirable to diagnose the allergy at the earliest possible stage, and then treat it as specifically as possible. A thorough diagnostic procedure with allergy in mind is necessary. Otherwise treatment in too many cases will be symptomatic, and only give temporary results. However, it is not to be denied, that diagnostic difficulties with a superimposed infection on allergy—sometimes only a latent or subclinical allergy—may be very great.

Without an improved technique for examination of discharge from the ear, an allergic otitis media may still be troublesome diagnostically to clear up. An allergic rhinitis is usually a clear diagnostic question, if it is not overlooked, but how many allergic antrums are not periodically washed out or even operated upon without a conscious suspicion of a possible allergy.

A valuable aid for diagnosing allergy of the nose is the nasal smear. Eosinophilia of the shock-organ is regarded as significant, and eosinophile cells in the smear or a histologic examination of biopsy material may give the answer.

A histological examination of the mucosa is not practical as a routine method. Examination of the nasal smear is very often a useful method, but is in many cases of limited value.

The main disadvantage of this method is that it cannot give the degree of eosinophilia in per cent. In a smear we too often find the eosinophile cells gathered in lumps in thickened portions of the smear, and from this to get a reliable impression of the real eosinophilia is impossible. If the smear is full of eosinophile cells, it may be of no importance, and the method is good enough, but in the many cases showing only a minor eosinophilia, it is not sufficiently reliable, and in such cases one is unable to tell if a real eosinophilia is present or not. Who is able to tell if there is only the normal amount of eosinophile cells or perhaps 8 per cent or even 12? And the indications for treatment may be dependent on a correct answer on such a question. At least it would be a very good help to have a correct answer.

Another disadvantage with the smear technique is that part of the eosinophile cells very often will undergo traumatic destruction, and the eosinophile red granules may be scattered. This may make an estimation of a possible eosinophilia more than difficult.

From the Ear, Nose and Throat Clinic, Lund, Sweden; chief, Professor G. Dohlman.
Dr. Stromme is now located in Oslo, Norway.

The staining technique is another difficulty. The nasal secretion may have a varying pH from case to case, different in acute and chronic cases, especially if a superimposed acute or chronic infection is present. The usual staining with Giemsa, May-Grünwald or Wright, delicately balanced polychrome stains, will often not offer uniform results, as the staining of granules, nuclei and cytoplasma varies very much with different pH.

The eosin-methylene blue staining advocated by Hansel is a great improvement in this respect.

In antral sinusitis the nasal smear technique is still less reliable, dependent as it is on secretion brought out through the ostium. The antral ostium may be periodically blocked, or the function of the cilia impaired due to infection. Using the result of antral washings for a smear means another disadvantage added to the other ones, because only a tiny portion of a rather heterogenous material is then examined at a time.

We wished to use the result of antral washings with a method which made it possible to determine the eosinophilia of the antral secretion in per cent.

Silverstolpe has advised a method for estimation of tumor-cells in sputum. The method is based on centrifugation in a centrifuge tube of special construction, making it easy to remove the sediment for further histological treatment, embedding it in paraffin. The narrowed-down bottom of the centrifuge tube is closed by a rubber cork. The top is closed by another rubber cork through which goes a capillary glass tube.

This "pipette-tube" of Silverstolpe has been found most useful for our purpose, and following the method of Silverstolpe to a certain extent we have modified it to serve our special purpose. In our effort to find a reliable method to differentiate the allergic sinusitis from the purely infectious one, we found it practical to examine the result of antral washings of out-patients at the clinic in the following way.

METHOD

The total "solid" result of an antral washing was collected in a graded test-tube. To this was added four times the amount of 8.7 per cent saccharose in physiological saline solution (blood-isotone) to get the mucus dissolved. To get a homogenous suspension the test-tube was carefully turned for a few minutes in order not to destroy the eosinophile cells.

The whole amount was then centrifugated for fifteen minutes at 2500 r.p.m. Then the sediment and lower clear portion of the suspension, totalling 8 ml., was transferred to the pipette-tube.

To this was added 1 ml. serum and 2 drops of Duboin's fixation-solution (20 ml. saturated sublimate solution, 5 ml. glacial acetic acid, 1 ml. formalin). After careful shaking this suspension was now centrifugated for twenty to thirty minutes at 3500 r.p.m. Then the bottom-cork was removed and the sediment plug, about 0.5 to 1 cm. long, was dropped into 95 per cent alcohol for fixation, and the usual histological treatment

with embedding in paraffin was done. The preparation was cut in the longitudinal direction with the sections 5 microns thick, and these stained with May-Grünwald and Giemsa (Pappenheim). As diluting solution for the Giemsa stain was used phosphate buffer of 6.8 pH.

RESULT

A histological section is obtained with the cells distributed rather evenly over the field of view, in one layer only, each cell distinctly stained. The eosinophile cells appear with the granules intensely red. All other elements are blue.

The leukocytes are as easy to differential count as an ordinary differential blood count.

COMMENT

The advantage of this method compared with the smear technique is obvious concerning exactness of result.

The histological section of the sediment looks like an ordinary tissue section, and every cell can be examined as clearly and distinctly as in a tissue section. In this histological section there are no mucous strings or lumps as in a smear, which too often blur the vision, hamper a distinct staining, and therefore make the examination too difficult and inexact. We get a practically even distribution of cells in the whole field of view. The staining of the smear is often very dependent on the pH of the secretion, a factor of uncertainty and variability. In the histological section, with the method advised, the staining is no problem at all; it is just as clear, distinct and unvariable as in an ordinary tissue section.

The disadvantage of the method is obvious too, and will limit its clinical use. The method is dependent on a laboratory with the necessary histological equipment.

The prehistological procedure can of course be done in any small laboratory equipped with a good centrifuge. The sediment plug can then in alcohol fixation be sent away for histological treatment.

With these clinical advantages and technical disadvantage, the method advised may be a useful diagnostical aid in selected cases.

SUMMARY

A cyto-histological method—based on Silverstolpe's technique for determination of tumor-cells in sputum—is advised to estimate a possible degree of eosinophilia in antral secretion.

The "solid" result of antral washings is homogenized, centrifugated, and the sediment treated histologically with the sections stained after Pappenheim. A 5 micron section shows the cells distributed evenly over the field of view, in one layer only, every cell distinctly stained. The eosinophile cells appear with the granules intensely red. All other elements are blue. The leukocytes are as easy to differential count as in an ordinary differen-

tial blood-count. A comparison between the smear technique and this cyto-histological method is given. The exact and reliable result of the method and the technical disadvantage are emphasized.

The method is recommended as a useful diagnostical aid in selected cases.

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ALLERGY TO COLD IN THE RESPIRATORY SYSTEM

Characteristics and Incidence in the Allergic Patient
An Experimental Study

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BEFORE Richet's experiments on anaphylaxis and von Pirquet's creation of the word "allergy," both physicians and laymen were aware of the fact that physical agents such as cold, heat, pressure and light could, in certain individuals, give rise to abnormal responses. Salter (1860) described a case of asthma after the application of cold to the feet. Behier (1866), Blachez (1872) and Negel (1884) were the first to describe cases of urticaria to cold.[5]

The considerable impulse given to the study of allergy at the beginning of this century led W. W. Duke to collect, in a remarkable synthesis, all the scattered observations under a common denominator which he entitled "Physical Allergy."[2,3] This book also presents a large number of cases of *specific* reaction to cold, heat, pressure and light.

However, the cases of allergy to light were set aside when it was proved that many of the patients had in their blood sensitizing substances of both the porphirin and other types,[9] which were the real cause of their photosensitivity. Also, sensitivity to pressure was seen to disappear on several occasions with the mere extraction of a septic focus, the cure of intestinal disorders, et cetera. Instead, attention was concentrated on allergy to cold, particularly after B. T. Horton suggested that many sudden deaths in the bath, swimming pool or river could be due to an anaphylactic shock.[7]

MECHANISM OF ALLERGY TO COLD

When relating his cases, Duke set forth an immunological theory for the purpose of explaining the phenomena. He suggested that the physical stimulus, when acting on the tissues of a hypersensitive individual, gives rise to a new protein possessing specific antigen properties (autogenous antigens). This explanation is supported by S. Karady's experiments,[11] as he was able to anaphylactize guinea pigs with their own serum, "cooled" *in vitro* at a temperature of —5° C. Duke's theory appears to be confirmed by Landsteiner and Chase's latest papers in which they claim to have obtained specific anaphylaxis by means of simple chemical substances linked to exogenous or endogenous proteins. In this case the cold either in a direct or indirect form, would play the part of a haptene; consequently it would be a form of autosensitivation of patients to their own modified proteins, in the same manner as psoriasis scales,[10] disorders of the ductless glands,[16] or epithelial desquamation.[6]

But immunological investigations show contradictory results. E. Rajka[13]

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managed to collect only thirty-six cases in the medical literature in which it is claimed that passive transmission of reagins to cold had been achieved; on the other hand, other authors (Jimenez Diaz, et cetera) emphatically state that they have never attained this, and neither have we in a typical case attended at the Instituto Nacional de Enfermedades Alérgicas (National Institute for Allergic Diseases). However, this might be due either to the fact that, because in order to react, the reagins require that the cold should become linked to or modify a skin protein (something which might not occur in all passive receptors), or to the fact that the sensitivity mechanism is not allergic. Urbach[14] believes that in many cases the mechanism is parallergic or simply a vasomotor disorder. This view is favored by the fact that, in certain people, the reaction appears when they come into contact with cold air but not with water or ice, and vice versa, or if the cold air is damp and not dry. In either cases the application of warmth immediately cancels the effect of the cold. Moreover, there are patients who react both to warmth and cold. Therefore, T. Lewis[12] believed that urticaria, for instance, is due to the H substance, which is produced by the skin when acetylcholine is freed by the endings of certain cholinergic nerves that he calls *nocifensors;* these nerves can also be excited by several other mechanisms besides the purely allergic one. As for the nature of this H substance, several authors[1,8] believe it to be histamine.

FORMS OF ALLERGY TO COLD

The best known and most common is urticaria to cold. Urbach and Gottlieb, who made a special study of it, state if a test to cold were carried out on many patients, the doctor would be surprised by the number of them who present urticaria through this means.[15] General phenomena are also mentioned as caused by cold, from hypertension to collapse and even death.[7] In the digestive system this agent may give rise to edema of the tongue, esophageal spasms, epigastralgia, colic and diarrhea; in the urinary system, to cystitis and nephritis; in the circulatory, to intermittent claudication, coronary stenosis and spasms of the blood vessels.

It is generally accepted that it is in the respiratory system where the cold affects a large number of the patients. All textbooks state that rhinitis, asthma and spasmodic cough can be caused by cold, and in this respect two possibilities are given: that the factor cold might be a releasing cause in an allergic patient, or that it might be itself the producing factor of the allergy, the latter occurrence being the less common of the two. But in the literature in general, the cases of the respiratory system, and also of the circulatory, digestive and urinary ones, are almost purely descriptive and clinical. With the exception of the aforementioned papers by Duke, it is very difficult to find indisputable cases of respiratory disorders released by cold *according to an allergic mechanism.*

It is because of this that we have planned this paper with the following goal in view:

TABLE I

No.	Name	Sex	Clinical Symptoms	Main Causes	Sensitivity to Cold	Pre-Test Examination			Post-Test Examination			Eosinophilic Index	Therapeutic Test
						Pulse	Rhinitis	Sibilant Rales	Pulse	Rhinitis	Sibilant Rales		
1	E.C.	F	Rhinitis	Room dust	−	78	−	−	76	−	−	0	Negative
2	R.S.	F	Asthma Rhin.	Multiple	++	80	+	+	102	+++	+++	10	Positive
3	N.I.	F	Rhinitis	Milk	+	88	−	−	90	++	−	9	Positive
4	T.C.	F	Asthma Rhin.	Room dust	−	100	+	+	88	+	+	0	—
5	M.L.	F	Asthma Rhin.	Catarrhal inf.	−	70	−	++	78	−	−	0	—
6	F.C.	M	Asthma	Multiple	−	76	−	+	80	−	+	0	Negative
7	C.R.	F	Asthma Rhin.	Room dust	+	100	−	−	92	++	+++	65	Positive
8	D.C.	F	Rhinitis	Wheat	−	86	−	−	72	−	−	0	—
9	J.F.	M	Asthma Rhin.	Room dust	−	88	+	+	88	+	+	2	Negative
10	D.S.	M	Asthma	Catarrhal inf.	−	80	−	+	80	−	+	0	Negative
11	J.M.	F	Rhinitis	Catarrhal inf.	−	110	+	−	110	+	−		Negative
12	E.S.	F	Rhinitis	Multiple	+	90	+	−	88	++	−	0	Negative
13	M.O.	M	Rhinitis	Multiple	−	88	−	−	98	−	−	0	Negative
14	M.G.	F	Asthma Rhin.	Multiple	−	76	−	−	76	−	−	0	Negative
15	A.M.	M	Asthma Rhin.	Milk	−	88	−	+	84	−	+	0	Negative
16	L.S.	M	Rhinitis	Butt. Choc.	++	64	+	−	65	+++	−	70	Positive
17	P.V.	M	Rhinitis	Multiple	+	64	+	−	66	+	−	4	Negative
18	C.A.	F	Asthma Rhin.	Multiple	+	96	+	−	96	+++	−	0	Negative
19	C.C.	M	Rhinitis	Multiple	++	78	−	−	78	−	−	0	Negative
20	E.V.	F	Rhinitis	Multiple	++	84	++	−	84	++	−	70	—
21	Z.C.	M	Asthma Rhin.	Multiple	−	76	+	−	76	+	−	0	Negative
22	A.M.	M	Rhinitis	Milk	−	88	−	−	80	−	−	0	—
23	J.S.	M	Pollinosis	Plane trees	−	72	−	−	72	−	−	3	Positive
24	O.S.	F	Rhinitis	Multiple	+	72	−	−	70	+	−	10	Negative
25	M.M.	M	Rhinitis	Multiple	+	72	−	−	70	+	−	4	Positive
26	M.A.	F	Rhinitis	Multiple	−	98	−	−	92	−	−	0	Negative
27	F.L.	M	Rhinitis	Room dust	+	76	−	−	76	−	−	0	—
28	J.B.	M	Rhinitis	Multiple	+	72	−	−	72	−	−	0	Negative
29	A.D.N.	M	Urticaria	Pressure	−	70	−	−	70	−	−	0	Positive
30	E.K.	F	Pollinosis	Compositae	−	68	−	−	66	−	−	0	—
31	L.S.	M	Pollinosis	Plane trees	−	71	−	−	70	−	−	0	Positive
32	N.N.	F	Asthma	Cold	++	82	−	+	80	+	+++	77	—
33	J.A.	F	Urticaria	Cold	−	66	−	−	66	−	−	0	Positive
34	Z.M.	F	Rhinitis	Multiple	+	77	−	−	74	−	−	0	—
35	A.M.	M	Asthma Rhin.	Catarrhal inf.	++	80	+	+	80	+	+	0	Negative
36	M.L.L.	M	Rhinitis	Room dust	−	75	−	−	75	−	−	0	—
37	F.F.	M	Rhinitis	Room dust	−	72	−	−	74	−	−	0	Negative
38	E.S.	F	Pollinosis	Compositae	−	81	−	−	78	−	−	0	Positive
39	M.B.	F	Rhinitis	Catarrhal inf.	−	77	−	−	82	−	−	0	Negative
40	M.J.	F	Rhinitis	Room dust	−	65	−	−	65	−	−	0	—

1. Find a practical method for detecting the sensitivity of the respiratory system to the action of cold.
2. Obtain an objective and easily carried-out test which will show the allergic character of the reactions.
3. Investigate the percentage of reactions to cold among a group of allergic patients.

METHODS

Our investigation has been carried out in forty patients with different allergic syndromes—mostly of respiratory character—who attended the "Instituto Nacional de Enfermedades Alérgicas" (National Institute of Allergic Diseases). We endeavored to study them during the remission stages of their symptoms, although this was not possible in some. The pulse and respiratory system of each patient were examined and three smears of nasal mucus were obtained. Immediately after they were asked to place both hands, up to the middle of their forearms, in cold water at a temperature of 0° to 3° C. for ten minutes; this was followed by a new examination and three more nasal mucus smears. The smears were stained with eosin-methylene blue[4] for the purpose of an eosinophile count; the percentage was calculated in relation to the total of non-eosinophile cells in the smear, whether they were leukocytes or not. The arithmetical difference between the pre-test and the post-test smears was called *cosinophilic index*, setting it arbitrarily as positive when it was higher than 3.

RESULTS

The results of our investigations appear in Table I. Under the heading "Sensitivity to Cold," + shows the intensity of respiratory symptoms that cold produces usually or occasionally on the patients; – when these symptoms are absent. The same applies to the heading "Rhinitis and Sibilant Rales." In the column "Therapeutic Test," we have indicated the results of the ingestion of antihistamine drugs (Benadryl, Antistine or Neo-Antergan, indistinctly). Those who did not make use of them are indicated by a line ——.

In Table II we have summarized the principal data.

COMMENTS

Forty per cent of the patients studied by us stated that they suffered from respiratory symptoms through the action of cold (wind, water, sudden drop in temperature); however, only 17.5 per cent showed any symptoms when tested by immersing their hands in water at 0° C. Two alternative reasons can account for this:

1. The method does not reflect faithfully the mechanism that gives rise to the symptoms, in which case the patients should be tested by placing them in a chamber where cold air can be circulated.
2. Those who react to the test are true allergic patients, and the rest

TABLE II. GENERAL SUMMARY OF TESTS TO COLD

	Totals	Percentages
Number of cases	40	
Male	19	
Female	21	
Stated to be sensitive to cold	16	40%
Stated to be insensitive to cold	24	60%
Showed respiratory symptoms with test to cold	7	17.5%
Showed no respiratory symptoms with test to cold	33	82.2%
Positive eosinophilic index (<3)	8	20%
Negative eosinophilic index	32	80%
Effect of antihistaminic drugs (therapeutic test) in patients presenting symptoms to cold		
Positive	5	83.3%
Negative	1	16.7%
Data in patients who showed no symptoms to cold		
Positive	5	22.F%
Negative	17	77.3%

would come within the group of the parallergics and of the vasomotor reflexes.

The symptoms of the allergy to cold were asthma, spasmodic cough and rhinitis with abundant hydrorrhea; these symptoms appeared either at the same time in a patient or separately. There was always a striking parallelism between the reactions to cold and the eosinophilic index. Only in Patient 18, who had shown intense rhinitis with hydrorrhea, there was not a higher index. On the other hand, Patients 17 and 20 presented no objective symptoms to the test and had an eosinophilic index of 4 and 70, respectively; the last patient stated that she had intense rhinitis when faced with cold wind. Former results show that the eosinophilic index has a twofold value: on the one hand it is an objective examination unaffected by the patients' statements, and on the other it is an indisputable proof that the symptoms appearing through the immersion in water at 0° C. is not a *vasomotor reflex but a true allergic phenomenon.*

All patients with a positive test to cold stated that these symptoms were usual in them.

Our attention was called to the fact that during the remission period hardly ever were we able to find eosinophiles in the nasal mucus of patients manifestly allergic, although the number of these cells increased sometimes by 70 per cent during the attacks of rhinitis and asthma, whether spontaneous or provoked. This finding leads us to recommend most warmly the method of hand immersion in cold water, not only for learning whether the rhinitis is allergic, but also for the purpose of starting the attack with the suspected agent, with eosinophile counts carried out before and after the test. In occupational allergy this investigation has been started already by J. Schcolnicov, and we believe it would be most profitable to extend it to other grounds.

The pulse examination did not prove useful, as many subjects had emotional tachycardia, and the pulse variations were not illustrative. Therapy with antihistamine drugs gave favorable results in nearly all those subjects with a positive test to cold, stopping the symptoms in some and avoiding their onset in others; however, when the cause of the disorders was not due to cold but to other sensitizations in those patients, those drugs were

unable to prevent the appearance of respiratory symptoms. Among the allergic patients with a negative test to cold, only the 22 per cent were benefited by antihistamine drugs, especially those with pollinosis.

We also wish to point out that Urbach and Gottlieb[15] emphatically state that skin allergy to cold is quite common; however, only one of our patients (who came to our institution with the diagnosis or urticaria to cold) showed signs of skin allergy.

Finally, we shall relate some complementary studies concerning the mechanism of the phenomena observed by us.

Mrs. R. S. said she suffered from asthma every time she washed clothes with cold water. The immersion test was performed and this promptly brought about an intense rhinitis with hydrorrhea and dyspnea with sibilant râles; this attack disappeared within one minute when her hands were placed in hot water. On another occasion, and without any explanation to her, before starting the experiment we applied a tourniquet on both her arms, above the elbows; no symptoms appeared. Two minutes after releasing the tourniquet, the original symptoms developed once more and were allayed by the immersion of hands in hot water.

On a third occasion, the attack of asthma was completely avoided by applying an intravenous injection of Antistine, a few minutes before starting the test. A few days later the patient was given a subcutaneous injection of 0.5 mg. of histamine phosphate; although it brought about an intense congestion of the head, cephalalgia and tachycardia, there was no rhinitis or asthma. This patient, sensitive among other things to room dust, potatoes and wheat, had her allergy to cold under control with Benadryl or Neo-Antergan; however, when she had asthma through another cause —viz., not due to cold—she reacted very little or not at all to antihistamine drugs, although ephedrine and elimination diets were of positive effect.

C. R. (No. 7) showed approximately the same type of symptoms as Mrs. R. S. Patient 16 (Mr. L. S.), besides being sensitive to butter and chocolate, was said to be also affected by cold. Immersion tests of the hands in water at 0° C. brought about an immediate response in the shape of intense rhinitis, hydrorrhea and an eosinophilic index of 70. The same test was carried out a few days later with a tourniquet round each arm; however, in this case, rhinitis appeared all the same. The injection of histamine phosphate gave rise to a severe congestion of the head, but there was no rhinitis. Later on the allergy to cold was controlled by antihistamine drugs, but the rhinitis due to butter and chocolate only disappeared with an elimination diet.

After a time (it was already summer), both Mrs. R. S. and Mr. L. S. did not show any reaction to the immersion of hands in cold water and their eosinophilic index was 0; it seems as if they had become spontaneously desensitized, at least for the moment.

Based on these three clinical histories, we feel we can state that there is nothing in them which proves that the symptoms are caused by the histamine arising from the tissues of the hands in contact with cold water. Although it is true that the said symptoms improved with the administration of antihistamine drugs, they were not reproduced by an injection of histamine. Besides, though in two cases the symptoms were not elicited when a tourniquet was applied to the arms, the reverse took place in a very definite case.

On the other hand, the rapid improvement experienced by the first cases when their hands were immersed in hot water, seems to suggest that there is a partial intervention of a vasomotor mechanism, perhaps through a discharge of epinephrine.

SUMMARY AND CONCLUSIONS

The authors studied the allergic manifestations to cold in the respiratory system of forty patients suffering from various clinical allergies.

Forty per cent claimed that the disorders were brought about by getting cold or wet, but only the 17 per cent showed objective symptoms (rhinitis, cough and asthma) with the test of immersion of hands in water at 0° C. during ten minutes.

The eosinophilic index, viz., the difference between the eosinophile content in the nasal mucus before and after the test, proved to be a most reliable and objective guide.

The presence of a large number of eosinophiles in the nasal mucus of patients that reacted to cold, show that the respiratory symptoms are due to a mechanism truly allergic and not to a vasomotor reflex.

Nearly all these patients benefited by the antihistamine therapy, providing they were not experiencing allergic symptoms due to other causes.

Skin manifestations to cold (urticaria) were rare.

This study does not support or deny that histamine or H substance is liberated in the tissues injured by cold.

Although it is supposed that only the 17.5 per cent of the allergic patients are sensitive to cold in a specifically allergic way, it is believed that before the above-stated figure is taken as a definite one, complementary tests should be carried out in chambers where cold air circulates at a certain speed.

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ALLERGY TO COLD AS AN OCCUPATIONAL DISEASE

Clinical and Experimental Study on 100 Workmen in Meat-Packing Factory

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THE studies mentioned in the preceding paper provided us with certain information on the fact that cold is capable of giving rise to allergic reactions in hypersensitive patients. Consequently, we became interested to learn how far the same physical agent is able to produce allergic reactions in patients selected at random. As with the former investigations we were unable to trace, in the available medical literature, a systematic study from the point of view of the allergic reaction to cold in general, but only isolated observations by Duke and to a certain extent by Urbach; however, these only referred to urticaria to cold (see previous article).

Hence the reasons for the present study which we believe has not been undertaken before from an allergic approach.

METHODS

Our investigations were carried out in 100 workmen employed at the Municipal Meat-Packing Factory of the City of Buenos Aires.* These subjects were taken at random from those who work in the freezing chambers (temperatures between -3° and -30°C) from one to six hours, with intervals of rest in between. At first we studied a group of sixty-five workmen (Group A) who had been carrying out their duties in these chambers for the last five to seven years (average 6.3 years); later we studied another group of thirty-five (Group B) who had been at the same task between two and five years (average 3.8 years).

After a short period of questioning to learn their allergic records and the symptoms usually experienced when entering the freezing chamber, each workman had his pulse taken and the blood pressure was registered in many; afterwards an examination of their respiratory system was performed and nasal mucus obtained for smears on a slide. After this the workmen entered the freezing chamber for their usual task; when they left an hour later the same procedure was carried out once more.

Thirty-two of the workmen in Group A stated that they usually experienced various symptoms when entering the chamber; they were given dragées of Neo-Antergan (N-p-methoxybenzyl-N-dimethyl aminoethyl-alpha-aminopiridine) to be taken daily, half an hour before work. A month later they were questioned as to the result. No placebo was given as control.**

*We wish to express our gratitude to Dr. Benigno R. Garat for allowing us to perform the study on behalf of the Instituto Nacional de Enfermedades Alérgicas (National Institute of Allergic Diseases), and to Dr. Francisco Pataro, Director of Technological Medicine of the Ministry of Public Health, who offered us every facility for our purpose. We also wish to acknowledge the co-operation of the authorities of the Municipal Meat-Packing Factory, of the CAP and especially, of the Staff Manager of the latter institution, Sr. Arana.

**We wish to thank the firm Quimica Rhodia for providing us with the necessary number of dragées of Neo-Antergan.

TABLE I. SUMMARY OF THE EFFECT OF THE FREEZING CHAMBERS ON MEAT-PACKING FACTORY WORKMEN

Group A	Totals	Percentage
Total of workmen	65	
Years of work in freezing chambers (average)	6.3	
With allergic antecedents	16	24.5%
Without allergic antecedents	49	75.5%
Stated to have symptoms to cold	32	49.2%
Stated not to have symptoms to cold	33	50.8%
Showed symptoms upon entering the freezing chamber	17	26.1%
Showed no symptoms upon entering the freezing chamber	48	73.9%
Positive eosinophilic index of the workmen who reacted to cold	14	82.4%
Negative eosinophilic index of the workmen who reacted to cold	3	17.6%
Response to antihistamine drugs of the workmen who reacted to cold:		
Positive	13	100%
Negative	0	0%
Response to antihistamine drugs of the workmen who did not react to cold:		
Positive	2	20%
Negative	8	80%
Group B		
Total of workmen	35	
Years of work in freezing chambers (average)	3.8	
With allergic antecedents	6	17.1%
Stated to have symptoms to cold	20	57.1%
Stated not to have symptoms to cold	15	42.9%
Showed symptoms upon entering the freezing chamber	10	28.5%
Showed no symptoms upon entering the freezing chamber	25	71.5%
Positive eosinophilic index of the workmen who reacted to cold	8	80%
Negative eosinophilic index of the workmen who reacted to cold	2	20%
General Results (Groups A and B)		
Total of workmen	100	
Years of work in freezing chambers (average)	5.3	
With allergic antecedents	22	22%
Without allergic antecedents	78	78%
Stated to have symptoms to cold	52	52%
Stated not to have symptoms to cold	48	48%
Showed symptoms upon entering the freezing chamber	27	27%
Showed no symptoms upon entering the freezing chamber	73	73%
Positive eosinophilic index of the workmen who reacted to cold	22	81.4%
Negative eosinophilic index of the workmen who reacted to cold	5	18.6%
Positive response to antihistamine drugs of the workmen who reacted to cold	13	100%
Negative response to antihistamine drugs of the workmen who reacted to cold	0	0%

RESULTS

A general summary of the results will be found in Table I. The column "Allergic Antecedents" contains those such as asthma, rhinitis with sneezing, urticaria and eczema, which the workmen had experienced outside working hours. In the columns "Stated to Have Symptoms to Cold" and "Stated Not to Have Symptoms to Cold" we have indicated whether the workman usually had abnormal symptoms when entering the freezing chamber for his daily work. The column "Eosinophile Index" shows the eosinophilic index obtained according to the method described in the preceding paper. Lastly, under the heading "Response to Antihistaminic Drugs" we have stated the results obtained with Neo-Antergan. Group B has no such column because the dragées were not given to these workmen.

COMMENTS

Of the 100 workmen studied, the 52 per cent stated to experience certain symptoms when entering the freezing chambers. The symptoms were chest oppression and dyspnea, rhinitis with sneezing or hydrorrhea, weeping, headaches, pains in bones or muscles, and, sometimes, epigastralgia

and cystalgia. These symptoms, which may appear jointly or separately, constitute a true *syndrome of disease by cold*, which may occasionally be seen in some people when merely exposed to a cold environment. On the other hand, we have never seen a single case of urticaria through cold in those workmen.

However, the examination practiced on the workmen revealed that only the 27 per cent of them showed objective symptoms; those who complained of headaches and cystalgias were not included because of the lack of objective symptoms. This percentage of 27 per cent is higher than that found in the group of allergic patients studied in our preceding paper (17.5 per cent). The reason for this may be either that the method of detection has provided a better reproduction of the usual conditions which bring about the symptoms, or that these patients are enduring more severe and repeated exposure to cold than the allergic ones. It is remarkable that among individuals taken at random there has been a similar or even greater number of allergic subjects to cold than among those patients who have a true allergic "diathesis," as it would seem more logical to expect a higher percentage among the latter. Nevertheless, the situation is rather similar to what happens in the serum disease or in cases of allergic reactions to drugs (sulphonamides), where the incidence is not greater among those individuals with allergic antecedents.

It is important to note that all the workmen with allergy to cold showed relatively mild symptoms, which, although troublesome at times, did not prevent them from working. Perhaps there may have been workmen who were more seriously affected with these symptoms, but it is likely that in that case they would have asked to be transferred to other sections.

An interesting fact is that among Group A (6.3 years of work in the meat-packing factory) and Group B (3.8 years) the incidence of affected workmen showed no appreciable difference. No relation was found between the type of symptoms and the lowest temperatures; on the contrary there was found a large proportion of workmen with symptoms among those who labored in atmospheres not so cold (-3° C.). Perhaps the only visible difference between Groups A and B is that among the latter the symptoms appear to be milder.

Examination of the pulse and blood pressure offered no interesting results. On the whole there was a decrease of both after the test, but this we believe was due to psychological reasons. The eosinophilic index was positive in the 81.4 per cent of the patients who felt symptoms in the freezing chamber. Instead it was always 0 in those who felt nothing; however, in one case of this type, eosinophiles were found in the smear. Lastly, thirteen of the seventeen patients who showed allergy to cold, took "Neo-Antergan." The 100 per cent felt an improvement, either moderate or marked. These were asked to attend the Instituto Nacional de Enfermedades Alérgicas (National Institute for Allergic Diseases) for the purpose of trying out a final course of treatment (histamine, histamineazo-

protein, progressive cold). Of the remaining workmen who had stated they experience symptoms in the chambers but without objective prove, two out of ten claimed a mild improvement with the therapy. We believe that most of these are not allergic to cold.

SUMMARY AND CONCLUSIONS

Fifty-two per cent of people who work daily in freezing chambers (at temperatures of -3° to -30° C.) stated to experience various symptoms when entering them (rhinitis, asthma, headaches, weeping and cystalgia); however, this was only detected objectively in the 27 per cent.

The symptoms were, in general, of moderate or mild intensity; they did not prevent the people from working, although at times they were of troublesome character. The symptoms appeared in individuals both with and without an allergic record; in those who had worked for the last six years, and those who had done so for only three, and in workmen who labored at -14° C. and also in those at -3° C.

The positive eosinophilic index was associated to allergy symptoms in the 81.4 per cent, and was negative in all the other patients.

The symptoms of the 100 per cent of workmen with allergy to cold improved partially or wholly with antihistamine drugs.

Allergists will be interested in new, versatile photomicrographic apparatus, designed also to serve other aspects of scientific photography. Known as the Orthophot, it provides facilities for photomicrography; photomacrography; micro-projection; laboratory, clinical, and general photography; photocopying; microfilming, X-ray photocopying; and photoenlarging. The apparatus is used with any standard microscope and consists of three basic units easily assembled for any use desired. The reflex camera itself is detachable and can be used on a standard tripod or hand-held for all forms of scientific or general photography. Those allergists who are interested in photography can obtain further information from Silge & Kuhne, Box AG, 153 Kearny Street, San Francisco 8, California.

A HEMORRHAGIC BULLOUS ERUPTION DUE TO PENICILLIN G

Relationship Between Chemical Structure and Sensitizing Capacity of Penicillin G and Penicillin O

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THE number of reports of serious reactions caused by penicillin sensitivity are becoming more frequent; however, as far as we are aware, no instance of a hemorrhagic bullous eruption has been reported in the literature.[2] Since the commonly used penicillin at present consists of penicillin G, it would seem feasible that a slight alteration in the chemical structure of penicillin may result in another penicillin which would exhibit antibacterial activity similar to penicillin G, without provoking a penicillin reaction in those individuals who are sensitive to penicillin G. The following case report deals with the clinical employment of such a penicillin:

M. C., a man, aged forty-four, was admitted on June 22, 1948, on the medical service at the Graduate Hospital with the chief complaint of pain in the legs, fever and general weakness. The past history included a "heart attack" three years ago and also one year ago. These attacks were characterized by sudden pain in the precordium following exertion. The pain lasted for one-half hour and did not disturb him unduly. There was no history of rheumatism, scarlet fever or chorea. About two months prior to admission, the patient began to notice pain in the legs which gradually became worse. Three weeks prior to admission he had to stop work. Accompanying the pain was generalized weakness. Two days before hospitalization the left ankle began to swell. There had been a weight loss of eighteen pounds in the past six weeks.

Examination revealed no dyspnea or cyanosis at rest. The heart was enlarged in the transverse diameter, particularly to the left. A rather rough, grating systolic murmur was audible at the apex (Grade III) and at the aortic area. The second sound was absent at the aortic area. The blood pressure was 105/40. The rhythm was regular. The lungs were clear. The liver was enlarged three finger-breadths below the costal margin, the spleen was palpable about two finger-breadths below the costal margin. No congestive phenomena were present. The temperature on admission was 100.2°, pulse 105, and respiration 24 per minute.

Roentgen examination of the chest showed generalized cardiac enlargement especially involving the left ventricle. The remainder of the examination of the chest was negative. Electrocardiogram on June 23 revealed evidence of myocardial damage and left ventricular hypertrophy.

The blood count showed a moderate anemia: red cells, 3,030,000; hemoglobin, 48 per cent; white cells, 7,100; 78 per cent neutrophiles, 20 per cent lymphocytes, 1 per cent monocytes. Except for a faint trace of albumin the urine was negative. Four blood cultures were consistently negative for streptococcus viridans.

The diagnosis in this case was rheumatic heart disease, cardiac enlargement, aortic stenosis, mitral insufficiency, probable subacute bacterial endocarditis. In view of the continued fever and the clinical findings in spite of negative blood cultures, a provi-

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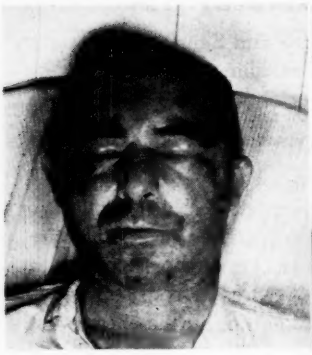


Fig. 1.

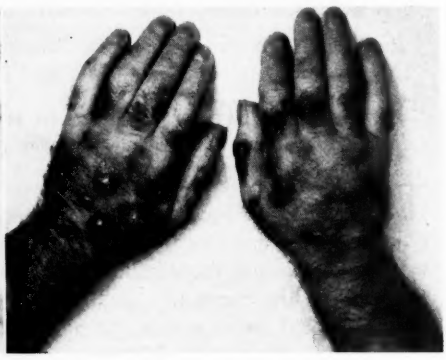


Fig. 2.

sional diagnosis of subacute bacterial endocarditis was made and penicillin was started. On June 24, 300,000 units of penicillin G were administered every three hours. The patient showed distinct clinical improvement, and the temperature dropped to normal in two days and remained normal during the rest of his stay in the hospital. His general condition and sense of well-being improved daily.

On July 8, petechiae 3 to 5 mm. in size were observed over the extremities and neck. They were purplish in color, hard in consistency and were associated with itching. On July 9 the patient developed on the face and dorsum of both hands tense bullae containing hemorrhagic exudates. This was accompanied by severe edema of the face, particularly marked in the infraorbital area. The impression was that this was a hemorrhagic bullous variant of an erythema multiforme-like reaction to penicillin, but since this patient had subacute bacterial endocarditis, and had been treated only fourteen days, the drug was continued another twenty-four hours, accompanied by 100 mg. of Pyribenzamine as the initial dose and 50 mg. every three hours.

The next day the reaction became worse (Figs. 1 and 2). There was complete closure of both eyes and massive swelling of face, hands, and scalp. Although the pruritus had been controlled, the bullous lesions became very tense or ruptured to form erosive patches. At this time, penicillin was stopped (July 9), 50 mg. of Benadryl were given every four hours, instead of Pyribenzamine, and boric acid compresses were applied to the eyes and to the areas of the ruptured bullae. The following day his condition was improved and there was reduction in the periorbital swelling. During the active phase of the eruption, fluid from one of the bullae was removed and injected into the skin of an individual not sensitive to penicillin. Forty-eight hours after this intracutaneous injection of the blister fluid, the recipient received 300,000 units of penicillin G. A reaction characterized by erythema, edema and papulization became manifest at the site of the previous intracutaneous injection (a positive Urbach-Koengstein test—implying the passive transfer of tissue antibodies). Normal control blister fluid at another skin site on the recipient gave a negative reaction.

This patient continued to improve clinically insofar as his drug eruption was concerned. No bullae appeared after penicillin was stopped, the edema and bullae gradually subsiding. The patient was discharged on July 24 much improved.

Because of the inadequate course of treatment for this patient (he had received penicillin for only sixteen days) and because of the unusual reaction to the drug, he was followed in clinic and his further course noted. For a short period of time there was a slow progressive improvement but this was soon followed by a return of his

original complaints associated with an elevated temperature. It was suggested that he be readmitted to the hospital to undergo a further course of the antibiotic, a penicillin which was allegedly free of allergic manifestations (penicillin O).*

The clinical findings were identical with those observed on the previous admission. The cardiac findings were similar to those mentioned above. However, his temperature on admission was 103° rectally, pulse 120, respirations 28 per minute. He was started on penicillin O, 100,000 units every three hours. His rectal temperature became normal after eight days and he felt well. On the sixteenth day he was noted suddenly to get into bed because he did not feel well, and shortly thereafter began to sweat profusely, vomited, and developed a left seventh nerve palsy, left hemiplegia, and dysarthria. In fifteen minutes he was comatose, with signs of decerebration rigidity, ankle and patella tonus, Babinski's and Hoffman's signs. The blood pressure was 230/70 (normally the blood pressure was 150/70).

Lumbar puncture revealed a spinal fluid pressure of over 500 mm. water; the fluid was grossly bloody. Three hours later he developed respiratory arrest and was put in an Emerson respirator with an endotracheal tube in place. His temperature started to rise. Nine hours after onset he died with a temperature of 108.°

Autopsy revealed a small pericardial effusion, moderate cardiac hypertrophy, moderate grade of aortic stenosis, and subacute bacterial endocarditis involving the aortic and mitral valves. These valves manifested vegetative and ulcerative lesions. Numerous emboli were observed in the spleen and kidneys. Rupture of a mycotic neurysm of the right leniculo striate artery, resulting in massive cerebral hemorrhage, was probably the immediate cause of death.

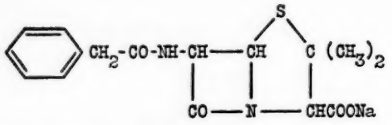
CONCLUSIONS

Hemorrhagic bullae have not been included among the drug eruptions caused by penicillin.[2] Inasmuch as this individual was shown to have subacute bacterial endocarditis, which itself produces hemorrhagic phenomena, it seems possible that these hemorrhagic phenomena combined with the manifestations of a severe penicillin sensitivity to produce the clinical picture shown by the patient.

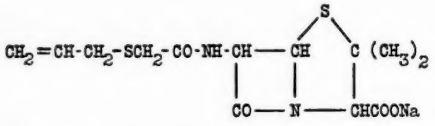
Various tests are available for evaluation of sensitivity to penicillin.[4,5] Unfortunately, no definite conclusion can be drawn from the results of such tests,[3,5,6] and occasionally, promiscuous testing may be dangerous and incapacitating for the patient.[7] The most reliable method is the readministration of the penicillin in question, and the observation of the patient's clinical course following this test dose. However, such a procedure was absolutely contraindicated in view of the severity of the previous cutaneous picture. The other reliable test to ascertain drug sensitivity is cessation of the suspicious drug, and if involution of the lesions occurs, it is presumptive evidence that that drug was the allergen. This criterion was satisfied in this patient. In addition, in this case the positive reaction to the Urbach-Koenigstein test was suggestive of sensitivity to penicillin G, while no reaction to the administration of penicillin O over a period of 16 days seems to indicate that this patient did not possess any sensitivity to penicillin O. Penicillin O differs from penicillin G in that the benzene ring of the latter has been replaced by the allylmercapto group.[1] In two

*Material supplied by the Upjohn Company, Kalamazoo, Mich.

other patients encouraging results were obtained with this new compound when it was used to replace penicillin G which had previously sensitized the patients.



Penicillin G, Sodium Salt (benzyl penicillin)



Penicillin O, Sodium Salt (allylmercapto methyl penicillin)

COMMENT

This patient in whom subacute bacterial endocarditis was suspected clinically, and later confirmed by necropsy, received routine treatment with penicillin G. Although the patient responded well to the treatment, penicillin administration was stopped before the course had been completed because of the development of a severe type of bullous eruption, which was due to his sensitivity to the penicillin. In the experience of one of us (S.B.), patients with aortic stenosis respond somewhat better than the average patient with subacute bacterial endocarditis to penicillin. In this patient, because of the inadequate course of therapy, incomplete healing occurred and the endocardial lesions continued to progress, resulting in death due to the usual embolic complications occurring in such patients. Although he was later started on penicillin O and tolerated this preparation without untoward effects, his condition had progressed to such a degree during the interval period where no treatment was given that he succumbed to the complications of the disease.

SUMMARY

The history of a patient with subacute bacterial endocarditis is reported who developed severe hemorrhagic bullous lesions during the course of penicillin therapy. Because of this complication penicillin was discontinued and the bullous lesions gradually disappeared. Due to the inadequate course of therapy, the infectious process progressed leading to death of the patient. This patient was later able to tolerate penicillin O without the development of allergic manifestations. This preparation was started sixteen days before death but was apparently unable to control the pro-

gression of the cardiac lesions, probably because of the long interval period during which the patient received no therapy.

In the presence of marked sensitivity to penicillin G, the use of penicillin O, because of the greatly lower incidence of allergic manifestations, may be administered and its use may be life-saving to the patient.

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HAY FEVER IN PALESTINE

(Continued from Page 349)

4. The number of hay-fever sufferers is far greater than previously indicated. Special attention is drawn to the clinically important observation that pollen was found to be the cause of asthma which recurred regularly each year in summer and autumn. Specific pollen treatment eliminated those symptoms.

5. The therapy which has been used by the author since 1929 consists of intracutaneous injections of pollen extracts prepared specifically for each patient. General mixed pollen extracts were less effective.

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AN INVESTIGATION OF THE ROLE OF FUNGI IN [illegible] WITH BRONCHIAL ASTHMA AND ANTHRACOSIS

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FORTY-SEVEN anthracite coal miners, who appeared for treatment in the allergic clinic and the medical wards* with complaints of various respiratory ailments associated with dyspnea, furnished the material for this study.

Since such workers suffer frequently from paroxysmal dyspnea characteristic of a bronchial asthma-like syndrome, an attempt was made to learn if these complaints might be due to certain occupational allergens, particularly fungi. A search was also made for individuals who were said to suffer from sneezing and lacrimination when exposed to certain sections of the coal mines.

Authoritative opinion indicated such underground locations satisfy the natural requirements for the growth of these organisms.

Later investigations have shown that the air of certain coal mines does contain large numbers of spores of *Penicillium (Pac) Zaleskii*** and a smaller number of spores of *Stysanus Stemonitis (Pers) Corda.* The fungi form a coat of mycelium several inches in thickness on the various types of timber used.

The following work was based on the concept of Courtright and Hurwitz† (1942-43), who confirmed Ratner's previous success in sensitizing guinea pigs to dry horse dander by inhalation. The fundamental principles underlying this observation are given by these workers as follows: "We agree that the inhalant method of sensitization approaches more closely natural sensitization of man than any other method.

"1. The allergen must enter the body through nasal or respiratory membrane or be held there.

"2. Sensitization is built up by repeated exposures which approximate more closely clinical sensitization.

"3. The respiratory mucous membranes, because of repeated exposure, may acquire resistance to general sensitization, which may not result from the subcutaneous or intraperitoneal routes."

In attempting to clarify the possible influence of atopic or acquired allergy arising from the aerial molds in the coal mines, the following study was undertaken.

A culture was obtained by exposing sterile Sabouraud's media petri

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Presented at the Fifth Annual Meeting of The American College of Allergists, April 14-17, 1949, Chicago, Illinois.

*The majority of these patients were subjects of a medical ward and allergy clinic of a general hospital situated in the heart of the anthracite coal region.

**Personal communication with Dr. Carroll W. Dodge, mycologist, Missouri Botanical Gardens, St. Louis, Mo., May 14, 1943. A tentative identification of the mold was made as *Penicillium (Paczeskii) Zaleskii.* Reference: Thom: The Penicillia, p. 202.

†L. J. Courtright, S. H. Hurwitz, and Abbie Betz Courtright: Inhalant sensitization of guinea pigs under controlled atmospheric conditions. J. Allergy, 13:271, 1942.

TABLE I.

Case Number	Years of Employment	Penicillium (Paczeskii) Zaleskii 100 pnu.	Penicillium (Paczeskii) Zaleskii 500 pnu.	Alternaria 100 pnu.	Aspergillus 100 pnu.	Household Dust (Conc.)	Ragweed 100 pnu.	Feathers (Mixed) 100 pnu.
1	5	−	−	−	−	+	−	−
2	11	−		−	−	+	−	
3	15	−	−	−	−	+	+	−
4	22	−	−	−	±	+	−	
5	23		−	−	±	±	±	
6	26		−	−	±	+	+	
7	28	−	±	±	−	++	++	+
8	30		−	−		+(+)	−	+
9	30		−	−	−	+		±
10	30		−	±	−	±	±	±
11	30		−	−	±	+(+)	±	±
12	30		−	−	−	+(+)	−	−
13	30		−	−	+	+	+	+
14	32	−	−	−	−	−		
15	33		±	−	−	+		±
16	38		+	−	+	+		
17	38	+	+	−	+	±(+)		
18	38	−	±	−	−	++	++	
19	39	±		±	−	+		
20	40	±	+	−	−	−	−	−

dishes to the air in different locations of an anthracite coal mine. Exposure was limited to fifteen minutes.

The number of colonies of fungi developing on each plate varied from five to fifteen. Transplants were made from the colonies of *Penicillium (Pac) Zaleskii* by inoculation into a medium consisting of crude dextrose four per cent, peptone one per cent, and tap water sufficient to make 100 per cent. The thick, fungous mat which grew on the surface of this liquid was collected, washed with 95 per cent alcohol and dried in a vacuum desiccator. Subsequent steps followed in the preparation of the extract were carried out in the allergy laboratory.

This investigation was begun in 1942.§ Twenty individuals were studied for hypersensitivity to the mold at that time (Table I). The method of procedure was as follows:

Intradermal injections were made with the extract of the mold in dilutions containing 100 and 500 protein nitrogen units per cubic centimeter. The quantity injected into the usual area of the upper arm was approximately .02 c.c. Reactions were recorded upon the expiration of a period of ten minutes. They were rated as slight when the wheal formed measured not less than one-fourth of an inch in diameter. Doubtful reactions were ascribed to those which had shown wheals less than one-fourth of an inch, or circular erythema not less than one-half inch in diameter. Reactions which came below these requirements were considered as negative.

Seven (30 per cent) of this group of twenty workers gave slight or doubtful reactions. Six of these were workers who had engaged in mining for from thirty-three to forty years. One had engaged in mining twenty-eight years. Thirteen had employment ranging from three to five years.

In attempting to substantiate the findings in this first group under study,

§) W. Piekarski: Study of sensitivities due to molds in an occupational environment. Read before the Central Pennsylvania Allergy Society, September 25, 1946, Lancaster, Pa.

TABLE II.

Case No.	Age	No. Years Employed	Penicillium (Paczeskii) Zaleskii 100 p.n.u.	Penicillium (Paczeskii) Zaleskii 1000 p.n.u.	Alternaria 100 p.n.u.	Aspergillus 100 p.n.u.	Household Dust (Conc.)	Mothy and Chard 0	Rag Weed 100	Feathers (Mixed) 100	Orris 100	Wool 100	Tobacco 1000
1	57	4	−	−	−	−	+	−	−	+	−	−	±
2	53	10	−	±	−	−	±	−	−	−	−	±	−
3	52	12	−	−	−	−	±	−	±	−	−	−	−
4	51	15	±	+	−	−	++	−	±	±	+	−	+
5	70	18	−	−	−	±	+	−	−	−	±	−	±
6	55	18	−	−	±	±	++	+	±	±	+	−	+
7	71	18	−	−	−	−	+	−	±	−	−	+	−
8	55	20	−	±	−	−	+(+)	−	−	±	−	−	−
9	64	20	−	±	−	±	−	−	−	−	−	−	−
10	66	21	−	±	−	−	++	−	−	+	−	±	−
11	51	25	−	±	−	−	++(+)	−	−	−	−	−	−
12	54	25	−	+	±	+	++	+	+	−	+	−	+
13	45	28	−	−	±	±	++	−	±	−	±	−	±
14	63	30	−	−	−	−	+	±	−	±	−	−	−
15	67	30	±	−	±	+	+(+)	−	−	±	−	−	±
16	48	30	−	±	−	−	+(+)	−	±	±	±	−	±
17	58	30	±	−	−	−	±	−	±	±	−	−	−
18	57	31	−	±	±	±	±	−	−	−	−	−	±
19	48	31	−	±	−	−	±	±	−	±	±	−	±
20	71	31	−	−	−	−	±	−	−	−	−	−	−
21	58	33	±	±	−	−	+(+)	−	−	−	−	−	−
22	56	34	−	±	−	−	−	−	−	−	−	−	−
23	67	36	−	−	−	±	±	+	+	+	−	+	−
24	62	36	±	−	−	±	±	−	−	−	−	−	−
25	65	37	−	−	−	−	+	−	−	−	±	±	−
26	78	47	−	−	−	−	++	−	−	±	−	−	±
27	70	50	−	−	−	−	−		−	−	−	−	−

the following recent investigations were carried out in 1947-48. On this occasion, twenty-seven subjects were studied (Table II).

Tests were performed with strengths of 100 and also with 1,000 protein nitrogen units per cubic centimeter of the Penicillium extract.

Evaluation of the skin reactions was made with a reasonable degree of accuracy considering the usual inconvenience met with in dealing with bed-ridden patients. Ambulant cases comprised about 50 per cent of the workers studied.

In view of the low-grade reactions in the direct skin tests, passive transfer was not attempted. Results of the skin tests in this second series were as follows: When an extract of *Penicillium (Pac) Zaleskii* was used containing 100 protein nitrogen units per cubic centimeter, doubtful reactions were observed in five out of twenty-seven (21.3 per cent) cases studied.

One of these doubtful reactions occurred in an individual who had been employed fifteen years. Fourteen individuals had been employed thirty or more years. Four of these gave doubtful reactions.

When an extract was used containing 1,000 protein nitrogen units per cubic centimeter, two (7.4 per cent) out of a total number of twenty-seven cases gave 1-plus reactions and ten (37. per cent) others gave doubtful reactions. The remaining fifteen cases (44.4 per cent) were negative.

The majority of these reactions began to appear after the twentieth year of employment when the stronger extract was used, as compared with the minimal period of thirty years when the weaker extract was employed.

Two paradoxical cases were observed which gave doubtful reactions with the weaker extract (100 protein nitrogen units per c.c.), whereas the stronger one (1,000 protein nitrogen units per c.c.) gave negative results. Such discrepancies may be accounted for either by technical errors arising from faulty visibility in some sections of the medical ward, or by differences in the reception of the skin as found in some cases when intradermal injections are made into the proximal and distal parts of the upper arm.

About one-fourth of this group, consisting of seven out of twenty-seven employes, had shown reactions in the skin tests of 2-plus grade to household dust and of a lesser degree to other common inhalants. In general, these cases also had shown other evidence of clinical allergy or had given positive histories of allergy in their ancestors or/and descendants. In most cases, the maximum period of their engagement in the industry did not exceed thirty years. It may be assumed that in some of these cases, employment was curtailed in a greater or lesser degree by dyspnea of an allergic nature, in which the clinical manifestations either preceded or were superimposed upon varying degrees of pulmonary fibrosis resulting from inhalation of mineral dusts.

About 75 per cent of the workers have discontinued their occupation for periods ranging from one to ten years prior to the beginning of this study.

In the survey of this investigation, the question arises as to what extent allergy to the occupational mold may be responsible for the attacks of

dyspnea? Whether the prolonged period of exposure to the concentrated atmospheric spores and other biologic structures of this organism had any influence on the skin tests in these cases is uncertain. Very likely, however, the skin manifestations were based on nonspecific reactions. According to vague results obtained in the latter procedure and failure to incite symptoms of bronchial asthma by insufflation of the environmental mold, the attacks of dyspnea are unlikely to be due to spontaneous or acquired sensitivities to the underground spores. On the basis of the foregoing studies it seems to be justifiable in assuming that the embarrassment of respiration in these cases is largely due to the following: (1) Fibrosis of the pulmonary tissues resulting from inhalation of mineral dusts which is accompanied by cor pulmonale in certain advanced cases.* (2) It may be due to upper respiratory infections commonly found in advanced cases of anthracosis.** (3) It is natural to assume that individuals showing moderate skin reactions to extrinsic factors, such as household dust, pollens, orris and feathers, may suffer clinical manifestations from this source. (4) Dyspnea due to other causes, such as foreign bodies in the respiratory tract, bronchogenic tumors, tuberculosis, et cetera, must be ruled out.

The essential findings of this study show the innocuous nature of concentrated atmospheric spores of *Penicillium (Pac) Zaleskii,* when inhaled by persons employed in the subterranean arteries for prolonged periods of time.

Another important feature brought out in this investigation relates to the use of penicillin as a therapeutic agent.

No unusual findings of an allergic nature, due to cross-reactions, were observed in these cases following its use as an antibiotic in the treatment of infections resulting from trauma or other causes. The use of this derivative of the genus, Penicillium, had met with the same degree of success in the treatment of those exposed to large numbers of occupational spores of this fungus as in persons of other walks of life.

In the limited number of cases presented in this report there were no histories referable to the ocular or nasal organs showing clinical manifestations of lacrimation and sneezing. Neither could these symptoms be elicited by insufflation of the occupational fungus under ordinary room temperatures. Whether or not a synergistic action of the fungus and the prevailing low temperatures of the underground locations plays a role in the production of these symptoms is open to further investigations.

SUMMARY

An investigation of the role of fungi in patients with bronchial asthma and anthracosis is reported.

The air of anthracite coal mines contains a large number of spores of

*Government bulletin: The Health of Workers in Dusty Trades. Exposure to Carbon Dust in Coal Mining. Survey of respiratory diseases in coal miners made during the period, January 1, 1924, to September 1, 1925.

**Physical examinations were performed on 344 coal miners. Findings recorded: bronchitis, 75; pleurisy, 3; pulmonary tuberculosis, 7; chronic rhinitis and pharyngitis in workers over forty-five years of age; pneumoconiosis, including anthracosis, 28; asthma, 9.

Penicillium (Paczeskii) Zaleskii and a smaller number of spores of *Stysanus Stemonitis (Pers) Corda.* These fungi thrive on nourishment derived from various kinds of timber and flourish with a luxurious growth of mycelium surrounding the ligneous structures.

A search for an acquired, or atopic, form of allergy due to occupational molds was made on forty-seven miners, most of whom were no longer employed for periods ranging from one to fifteen years, due to physical disabilities resulting from anthracosis with manifestation of bronchial asthma-like syndrome.

The study was made in two series. The first group was composed of twenty and the second consisted of twenty-seven unemployed persons with anthracosis. The first study was made in 1943, and the second in 1948.

The purpose of this investigation was primarily to learn if any atopic allergies existed to the inhaled spores of the occupational mold; also, whether or not, skin sensitization can be produced by inhalation, for long periods of time, of large numbers of spores of this fungus.

Observations were also made for symptoms expressed clinically in lacrimation and sneezing, said to be present in certain underground workers at times when they are exposed to an excessive growth of fungi.

Intradermal tests were made and the dried powdered mold was insufflated in the second series of workers studied.

In the first series of workers studied, the extracts used in the intradermal tests consisted of 100 and 500 protein nitrogen units. There seemed to be some correlation between the time of appearance of doubtful reactions in the skin tests and the period of exposure to the mold. All anthracotics whose time of employment in the coal mine exceeded thirty-two years showed such reactions. Six reactions were noted.

In the second series, the results were more disappointing. Only four out of fourteen patients whose former engagements in the industry exceeded twenty-eight years gave doubtful reactions in the skin tests, when an extract containing 100 protein nitrogen units per c.c. was used.

With the use of an extract containing 1,000 protein nitrogen units per c.c., eleven skin reactions were noted and they were nearly all doubtful. No uniformity existed as to the time of exposure and the appearance of doubtful skin reactions. Like the remainder of these tests, they were apparently based on nonspecific origin.

27 East South Street

IDIOBLAPTIC TOBACCO SENSITIVITY

GRANVILLE F. KNIGHT, M.D., F.A.C.A.
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THE substances to which the human body may react in an abnormal or hypersensitive manner would seem to be legion.

The use of tobacco by a large proportion of our adult population in homes, offices and public places results in the widespread exposure of most people to tobacco smoke. It is not surprising, therefore, that a certain number of smokers and nonsmokers should report unpleasant reactions of varying severity from this contact.

In view of these reports it is of considerable importance to determine, if possible, the incidence of tobacco hypersensitivity, and to catalogue any harmful symptoms attributable thereto.

A quick review of the literature reveals a wide divergence of opinion as to the potentially harmful effects of smoking tobacco.

A number of observers[3,6,7,9] have shown that in many individuals, smoking is accompanied by a temporary tachycardia, rise in blood pressure, elevation of the blood sugar, drop in peripheral temperature, changes in the electrocardiogram (arrhythmias and prolongation of the QRS interval) and decreased oxygen utilization by the superficial tissues.

Analogous changes have been produced by intravenous nicotine.[6,7]

Harkavy[5] demonstrated to his own satisfaction positive skin tests and the presence of tobacco reagins in 55 per cent of eight cases of thromboangiitis obliterans.

Hewell[6] could not demonstrate positive skin tests in any cases studied by him. In a thorough study of twelve individuals he noted a tachycardia and rise of blood pressure in all. He explained this on the basis of idiosyncrasy to a common substance affecting certain individuals who have labile vascular systems. A few of his subjects did not react.

H. L. Segal[8] reported six patients with chronic fatigue relieved by cessation of smoking. All had a pulse rise with smoking. He did not attribute this picture to any idiosyncrasy.

H. G. Hadley[4] in a study of pulse and blood pressure in 7,000 office patients, concluded that the tobacco habit increases the pulse rate but lowers the blood pressure. His observations are open to the criticism in that he included in the smokers group those who had smoked even one cigarette within three years!

Coca[1] has recently stressed the fact that while many smokers show a tachycardia and rise in blood pressure following the use of tobacco, a considerable number fail to show any observable change. He attributes this difference to the presence of nonreaginic allergy in the reactors.

The following observations were carried out, independently, after contact with Coca's work on nonreaginic food allergy in 1943. Until recently,

Presented at the Fifth Annual Meeting of the American College of Allergists, April 14-17, 1949, Chicago, Illinois.

acquaintance with the literature was purposely avoided so that preconceived ideas might not be acquired.

In attempting to work out problems of food allergy, according to pulse response, it was soon realized that tobacco itself was a major and, in some

PULSE CHART

DATE_____ NAME_____

TIME	PULSE	DIET	SYMPTOMS
BEFORE RISING		BREAKFAST	
BEFORE BREAKFAST			
½ HR. LATER			
1 HR. "			
1½ HRS. "		LUNCH	
BEFORE LUNCH			
½ HR. LATER			
1 HR. "			
1½ HRS. "		DINNER	
BEFORE DINNER			
½ HR. LATER			
1 HR. "			
1½ HRS. "		TOBACCO USED	
AFTER RETIRING			

DIRECTIONS

(1) COUNT PULSE FOR ½ MINUTE AND MULTIPLY BY 2.
(2) EXCEPT FOR THE MORNING AND EVENING, SIT DOWN FOR 3 MINUTES BEFORE TAKING PULSE.
(3) RECORD DUSTING HOUSE, CONTACT WITH PAINT FUMES, SOAP POWDER, SCENTED COSMETICS, OR ANY UNUSUAL ACTIVITY.

G. F. KNIGHT, M.D.

Fig. 1. *(A)* Pulse chart.

cases, the sole offender. Its ability to produce a persistent tachycardia throughout the waking hours of certain smokers, together with potentially serious symptoms, was deemed sufficient reason for this preliminary report.

METHODS

Observations were made on private patients who came to the office complaining of conditions which might be classed as allergic, as due to chronic infection, or a combination of the two.

Preliminary work included a careful history, physical examination, skin tests and laboratory work as indicated. Intradermal tests to tobacco were either negative or doubtful. No passive transfer studies were undertaken.

At the first visit, pulse and blood pressure readings were taken after the patient had been sitting down for five minutes.

All blood pressure readings were made from the right arm, with the same machine and by the same observer.

Any patient with a pulse rate over 72, a blood pressure higher than an arbitrary 126/76, or with a history suggesting idioblapsis, was asked to chart his pulse rate for a period of forty-eight hours and to list all food and drink taken. Readings were recorded before arising and after retiring, before each meal and three times afterwards at half-hour intervals. With the exception of the first two, which were recorded prone, the subject was asked to remain seated for three minutes before taking his pulse. Instruc-

tions for taking the pulse were given and the patient's readings checked.

For the purposes of this paper only smokers were included.

At the second visit the significance of the pulse chart was explained and

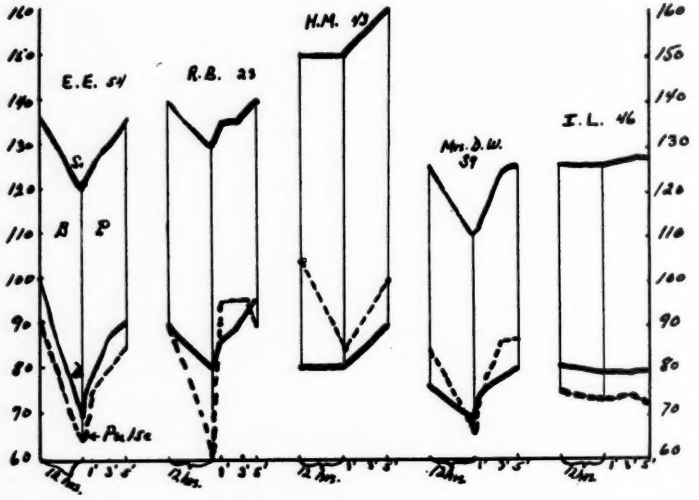

Fig. 1. *(B)* Various types of reaction to the smoking test.

pulse and blood pressure determinations again made. Tobacco consumption was estimated.

Those with charts showing a spread of 20 or more beats between the highest and lowest recorded pulse rates, or with a high which surpassed 90 were assumed to be allergic to tobacco, to foods or to other factors in the environment.

Patients willing to co-operate were then requested not to smoke after 10:00 p.m. and told to report the next morning between 10:00 and 12:00 a.m. This hour was chosen to rule out the possible effect on the pulse rate of foods taken at breakfast. Charting was continued.

SMOKING TEST

At this visit the patients had not used tobacco for twelve hours, and the great majority showed a significant drop in pulse rate and blood pressure. These readings were taken as usual after five minutes in the sitting position.

Patients were then asked to smoke a cigarette. Pulse and blood pressure were recorded at one, three, five and ten-minute intervals.

Early observations in sensitive individuals showed the tachycardia to begin within ten to thirty seconds and to reach its peak in three to five minutes. When a rise in blood pressure occurred, this roughly paralleled the pulse acceleration.

While Coca has postulated that subcapsular kidney edema may account

for idioblaptic hypertension, the rapidity of the response to tobacco suggests that overactivity of the sympathetic nervous system and perhaps the adrenal medulla, with resultant vasospasm, may be of more importance.

If a definite rise of 10 points or more in pulse rate was noted while

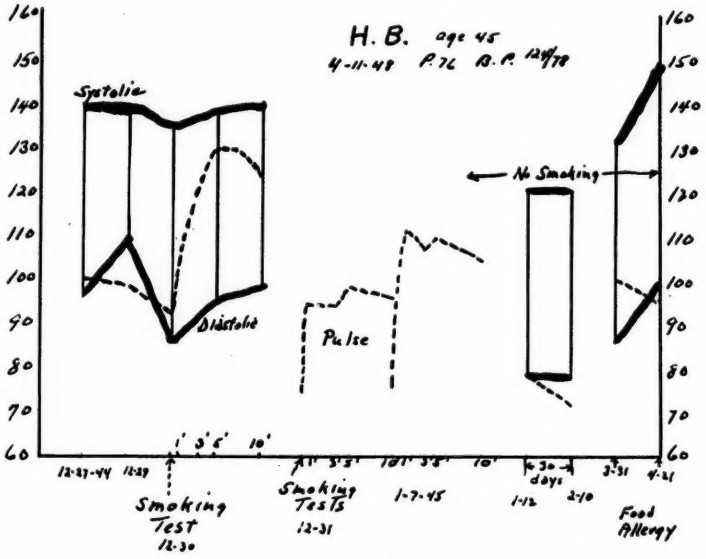

Fig. 2. Case 1. Marked tachycardia of at least ten years' duration, fatigue, nervousness and moderate hypertension relieved by cessation of smoking. Marked pulse reaction to tobacco. Recurrence due to food allergy relieved by elimination of offending foods.

smoking, patients were asked to stop tobacco, or to cut down cigarette consumption to a maximum of six taken between meals and during the evening and to continue with the pulse chart.

The effect of the new regime on the pulse was noted for forty-eight hours more and recorded by the patients. At the end of this time repeat observations were carried out in the office. Inquiries were made to bring out any changes which might have occurred in symptomatology.

GENERAL OBSERVATIONS

In many cases, restriction of tobacco resulted in a marked drop in pulse rate. Concomitant with this, there was noted in certain individuals a significant drop in blood pressure and/or relief from unpleasant symptoms. The following are worthy of mention: tachycardia, palpitation, extra-systoles, fatigue, depression, headache, vague fear sensations, insomnia, nervousness, tremor, post-nasal drip and stuffy nose, sleepiness in the afternoon, morning tiredness, tickle in pharynx and larynx, chronic cough, chronic bronchitis, gingival irritation, coated tongue, mild parotid swelling, hoarseness, neuralgic pains, cervical and interscapular myalgia or "tightness,"

weakness of legs, joint pains and stiffness, constipation, decrease in olfactory and visual acuity. Other phenomena will undoubtedly be reported.

CASE HISTORIES

Case 1.—Mr. H. B., aged forty-three, was first seen December 27, 1944, complaining of post-nasal discharge and recurrent sore throat of two to three months' duration. History revealed the following: Subject to fall hay fever. Tonsillectomy and ade-

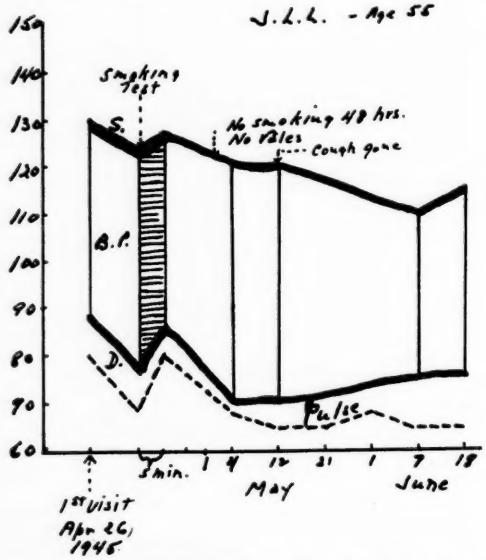

Fig. 3. Case 2. Severe morning and evening physical tiredness, much post-nasal drip, and more or less continuous wheezing and coughing for twenty years. Complete relief by avoidance of tobacco.

noidectomy as child. Remains treated with electric needle. Right antrum irrigated ten years ago. Rapid pulse since childhood; as high as 140 thirteen years ago, at which time vision in left eye decreased rapidly. Thyroid brought pulse down to around 100 and relieved the visual loss. Taking 5 grains of thyroid daily past ten years. Smokes about ten cigarettes in twenty-four hours.

Physical examination: Pulse 100, blood pressure 140/96. Antra dark. Tonsil fragments and linguals cryptic and inflamed.

Impression: Sinusitis, tonsillitis, hypertension, nonreaginic allergy.

Local condition improved with penicillin therapy to sinuses.

Pulse chart showed range of 68 to 136.

A smoking test after twelve hours' abstinence from tobacco showed a brisk reaction (Fig. 2).

He was advised to stop smoking and did so by the end of one week.

His pulse and blood pressure stabilized at normal levels as shown in the diagram, and he reported much less fatigue and increased muscular power as well as decreased nervous tension.

He came in again almost three months later, complaining of fatigue and the jitters and that his pulse was up again. He attributed this to lack of thyroid, his dose having been cut to 2 grains daily.

A marked tachycardia and definite hypertension were again present. By means of a trial diet it was shown that sensitivity to a number of foods was now causing trouble. Elimination of these resulted in a relatively normal pulse and blood pressure which have persisted.

Last seen April 21, 1948. Pulse 76, blood pressure 124/78. Still gets occasional rise in pulse and blood pressure, especially in mornings, apparently from some inhalant allergen.

It is noteworthy that his hay fever was not relieved by this regime.

Case 2.—Mr. J. L. L., aged fifty-five, came to the office on April 26, 1945, complaining of much post-nasal discharge, more or less continuous wheezing and coughing and marked morning and evening fatigue over a period of twenty years. Worse past eight years. Weight loss, 10 pounds in past three years.

Past history revealed a family history of hay fever and asthma. Operation twenty years ago for carcinoma of epididymis. Much x-ray therapy. Checked seven years ago; apparently all right. Alcohol, about one drink monthly—more than one knocks him out. Used to smoke one pack of cigarettes—now about one-half pack.

Physical examination: Audible wheezing and bubbling râles. Stethoscope revealed coarse, moist râles both lungs. Pulse 78, blood pressure 126/80. Pulse chart lost.

A smoking test after avoidance of tobacco for twelve hours showed a comparatively slight, but as results proved, a significant reaction (Fig. 3). Avoidance of tobacco was advised.

Examination on May 1, 1945: No smoking, No audible râles. Cough better. Chest x-ray shows increased markings. His cough rapidly disappeared, his excessive fatigue vanished and he gained weight. He found that, much to his surprise, he could now take two or even three drinks on occasion without severe ill effects.

When last seen two years later at a social affair he reported that he was well and that the cough had not returned.

Case 3.—Mr. D. C., aged thirty-nine, a lawyer, was first seen in 1941 complaining of stuffy ears. Questioning revealed the presence of rather profuse, whitish nasal and post-nasal discharge, most marked upon arising. Mild psoriasis noted for five years. Diet satisfactory. Smoked one and one-half to two packs cigarettes daily. Alcohol used to mild excess over week ends. Worked under considerable pressure.

Physical examination: Pulse 70, blood pressure 115/80. Looks well. Nasal mucosa slightly pale and boggy. Examination otherwise negative except for coated tongue.

Skin tests to staple foods and a few common inhalants, including tobacco, were negative except for a slight reaction to tea and coffee.

Dietary management and removal of ear wax resulted in slight improvement in nasal symptoms and relief of ear complaints.

The patient returned two years later in June, 1943, for removal of wax. Post-nasal discharge worse, coughing in mornings sometimes inducing vomiting.

Physical examination: Pulse 80, blood pressure 150/100. Tongue shows marked yellowish coat. Wax removed. Laboratory work negative.

One week later: Pulse 96, blood pressure 146/96.

Pulse chart showed top rate of 96.

Advised to stop tobacco and alcohol and chart pulse.

Three days later pulse from 54 to 64, blood pressure 115/80. Cough and morning discharge 80 per cent gone. Tongue almost clean.

On June 26, six days later, the blood pressure was 130/80.

One June 29, nine days later, it was 110/60. Almost no cough or discharge.

A study of Figure 4 shows the effects of resuming alcohol a few days after starting the trial diet. While food allergens were suspected when his pulse rose into the

70's, none could be demonstrated. It must be assumed that a carry-over from alcohol was responsible. The slight drop in pulse rate between (5) and (6) on the chart, when alcohol was stopped, is suggestive.

After a smoking test (8) this patient would no longer keep a chart, and the

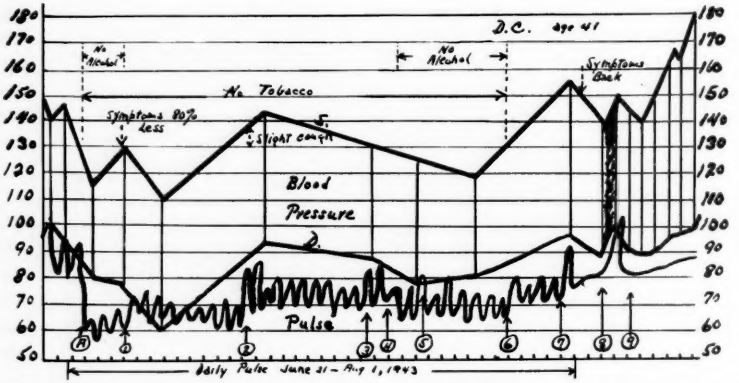

Fig. 4. Case 3. Disappearance of tachycardia, hypertension, excessive fatigue, cough and marked post-nasal drip following elimination of tobacco and alcohol, together with their reappearance upon renewed contact with these substances.

(A) Nothing except water after lunch. (1) 1 or 2 drinks daily. (2) 2 to 6 drinks daily. (3) After tennis. (4) Stopped alcohol. (5) Important business luncheon. (6) 2 or 3 drinks daily, plus 2 or 3 cigarettes. (7) Resumed smoking. (5 to 15 cigarettes) Old symptoms back. (8) No smoking five hours. Smoking test. Reading after 5 minutes on August 27, 1943. (9) Vertical lines indicate sporadic observations on September 17 and 30, 1943; December, 1944; October and November, 1945; August, 1946.

subsequent readings were made in the office when he appeared for treatment of colds or removal of wax.

At the last visit there was a marked tremor of hands, lips and tongue. The latter showed a heavy yellowish coat.

It is worthy of note that in spite of the evidence incriminating tobacco and alcohol, this patient refused to give them up. The psychological reason could not be uncovered, nor would a psychiatrist be consulted. The implications are challenging.

INCIDENCE OF TOBACCO SENSITIVITY

Time has not permitted a survey of all smokers tested. However, sixteen of the first 100 cases, or 16 per cent, failed to show any pulse response to the smoking test.

This figure differs considerably from Coca's report[1] of tobacco sensitivity in thirty cases solved by the pulse method. Here he found a specific tachycardia from tobacco smoke in only 50 per cent.

This marked discrepancy may be due to two factors:

1. The difference in the number of cases surveyed.

2. A summation effect, in the present series, of sensitivity to foods, alcohol, inhalants and tobacco.

For instance, it has been observed in several cases that ingestion of moderate and excessive amounts of alcohol the night before results in a higher

pulse rate the next day. The pulse response to tobacco in sensitive individuals is much more marked in the presence of this carry-over from alcohol.

Coca's cases, when tested to tobacco, were not under the influence of other allergens.

More work on this phase of the problem is indicated.

DISCUSSION

Unfortunately, many patients, sensing a frontal assault upon one of their ingrained habits, either retired disgruntled from the field or insisted upon treatment without further investigation of their tobacco sensitivity.

The majority were co-operative as far as the preliminary survey was concerned. But, unless suffering from very uncomfortable symptoms, or possessing unusual intelligence and fortitude, they refused to give up tobacco indefinitely.

Be this as it may, a number of sensitive individuals were impressed by the objective evidence shown by the pulse charts. These were helpful in upholding the analogy between an unnecessarily rapid pulse rate and the racing motor of a car with a slipping clutch.

It may be that in the future with increased knowledge of harmful effects from tobacco smoke, the physician can be firmer in his advice that sensitive patients should stop smoking. This would apply particularly to those with clinical signs or symptoms that have been found to be associated with idioblapsis.

SUMMARY AND CONCLUSIONS

1. While some individuals may smoke tobacco without any obvious cardiovascular response, others exhibit a specific tachycardia. This increase in pulse rate may be accompanied by unpleasant and potentially dangerous symptoms which, unless due to idioblaptic allergy to other contactants or ingestants, or to irreversible changes, disappear with cessation of smoking. It seems logical to describe the reactors as allergic to tobacco smoke.

2. A simple and practical method of discovering this sensitive group is described.

3. Many smokers use tobacco frequently enough to maintain a tachycardia throughout their waking hours. While not all of these will complain of symptoms referable to the use of tobacco, it seems unlikely that overstimulation of the cardiovascular system over a period of years can be considered harmless to the human homeostatic mechanism.

4. Allergic individuals should be advised to stop smoking or to limit their consumption to the equivalent of six or eight cigarettes daily. Moderation seems to be impossible for most of this group.

5. Hypersensitive patients who do stop smoking should, for a period of six to eight weeks, fill out a twenty-four-hour pulse chart once weekly in

(Continued on Page 431)

MICROPOWDERED PROCAINE PENICILLIN BY INHALATION

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DURING the past year, there has been widespread clinical use of procaine penicillin by injection.[2,3,4,12,13,14,22,29] The chemical combination of procaine and penicillin G, mole for mole, results in a true salt which retains the antibiotic activity of penicillin as well as some of the local anesthetic properties of procaine.

Procaine penicillin is a white substance with a characteristic crystalline structure. It is relatively insoluble, non-toxic, and non-irritating to body tissues or mucous membranes. If this compound is micropulverized and suspended in oil or aqueous solution, the resulting suspension is absorbed at a slow rate after intramuscular injection. Blood concentrations in a therapeutic range have been consistently attained for twenty-four hours or longer. If the same substance is mixed with a water repellent, such as 2 per cent aluminum monostearate, the individual particles are coated and the rate of absorption is decreased. Thereby the interval between injections may be greatly prolonged. Procaine penicillin is considered to be the most satisfactory repository type preparation now available commercially. This is particularly true when the crystals have been reduced to a fine powder (5 microns or less) prior to suspension in a vehicle containing aluminum monostearate.

Because of the properties of procaine penicillin mentioned, it was decided to investigate the use of microcrystalline procaine penicillin by inhalation. Preliminary studies revealed that such powders were almost odorless, tasteless, and non-irritating to the nasal and pharyngeal mucous membranes. Prior to extensive clinical trial, bacteriologic assays were made to measure the absorption rates of procaine penicillin from the respiratory tract following oral and intranasal inhalations. It was soon observed that the rates of absorption are two to four times slower compared with those following sodium penicillin preparations having approximately the same particle size distribution. For example, 100,000 units of procaine penicillin gives detectable blood levels for six to eight hours compared with two to three hours following the intranasal inhalation of sodium penicillin.

The major purpose of these preliminary investigations with procaine penicillin micropowders was to determine the incidence of allergic reactions, both local and systemic. Inasmuch as procaine itself is an allergen,[20] it was necessary to demonstrate clinically whether inhaling the chem-

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ical combination of procaine and penicillin caused more allergic reactions than the inhalation of pure crystalline sodium or potassium penicillin salts. Although the incidence of allergic reactions after intramuscular injections of procaine penicillin is not reported to be higher than that following intramuscular administration of sodium penicillin in saline solution,[6,8,15,19,23] it was essential to demonstrate whether the same relation existed following inhalation therapy.

TABLE I. PARTICLE SIZE DISTRIBUTION OF THE MICRO-POWDERED PROCAINE PENICILLIN PREPARATION USED*

Size Range (Microns)	No.	Number Per Cent	Surface Per Cent	Weight Per Cent
Below 1	46	15.3	0.24	0.02
1-2	92	30.7	1.40	0.16
2-3	31	10.3	1.45	0.28
3-4	14	4.7	1.30	0.36
4-5	18	6.0	2.85	1.01
5-10	61	20.3	29.42	18.80
10-15	27	9.0	31.80	31.07
15-20	8	2.7	19.94	28.09
20-25	3	1.0	11.58	20.21

Note: 300 particles were counted with the light optical microscope at 970 magnification using immersion oil on both surfaces of the microscope slides.
*Generously supplied by the Lederle Laboratories, Division of American Cyanamid Company.

PARTICLE SIZE DISTRIBUTION

Light and electron microscope examinations were made to determine the crystalline structure and the particle size distribution of this preparation. The mean particle size computed by numbers was found to be 1 to 2 microns, whereas it was much larger when computed by surface area and weight (Table I). The crystalline structure is shown in Figure 1.

RESPIRATORY TRACT RETENTION

After the intranasal inhalation of procaine penicillin powders, the expired air may be measured for penicillin content by immediately exhaling into a measured volume of buffered saline through a glass tube containing an absorbent cotton filter. Also, by gargling with measured amounts of saline immediately after each inhalation, the amount of penicillin deposited in the mouth and pharynx may be estimated by assaying these washings for penicillin.[24] The results of these experiments demonstrate that more than 99 per cent of the inhaled dose is retained in the respiratory tract. The greatest portion is deposited in the nasal passages.

The particle size distribution of the crystals present in the exhaled air may be demonstrated microscopically by exhaling directly on to a microscope slide and covering the mist-laden area with a coverslip. Most of the exhaled procaine penicillin may be seen to consist of extremely fine particles measuring 1.0 micron or less, and a few particles approximately 2 to 3 microns, greatest dimension. This observation is in accord with the work of Hatch, et al, who have shown that for complete pulmonary penetration

and maximum alveolar retention dusts must include a particle size range varying between 0.2 and 2 to 3 microns.[11]

CLINICAL MATERIAL AND DOSAGE SCHEDULES

The majority of patients studied were adults of both sexes, twenty to sixty years of age. The following types of infections were treated: acute

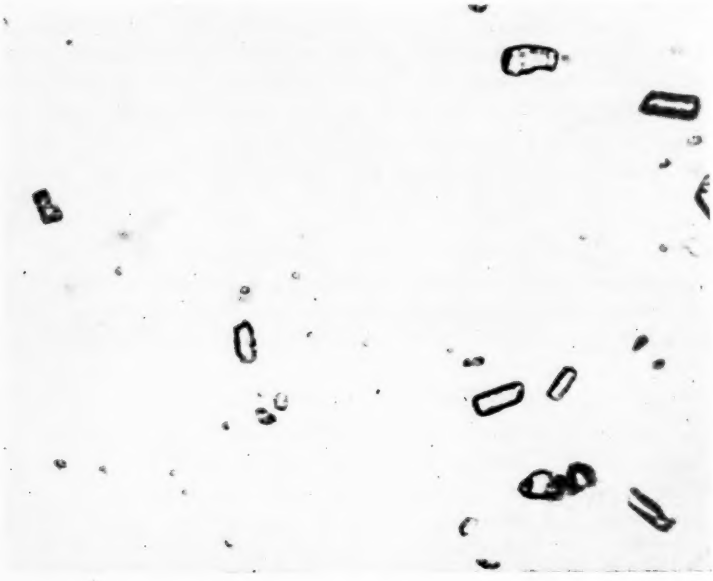

Fig. 1. Photomicrograph of procaine penicillin micropowder demonstrating characteristic crystalline structure. Magnification 600 times.

nasopharyngitis, acute and chronic bronchitis, acute tonsillitis, acute sinusitis, acute and subacute cervical adenitis, acute laryngitis, and chronic bronchopulmonary disorders—primarily bronchiectasis with and without asthmatic manifestations.

The percentage of allergic individuals included was greater than that occurring in the general population. Also several cases of asthmatic bronchitis and bronchiectasis with associated allergic asthma were purposely treated. All patients were questioned as to the presence of common allergic manifestations, the occurrence of previous penicillin sensitization, and any history of untoward reactions immediately following the injection of procaine solutions. A record of any penicillin therapy administered during the past two years was also kept.

In the treatment of acute respiratory infections, the average dosage schedule used was 100,000 units inhaled two or three times daily for two to five days. The same dosage was given for seven to fourteen days for

TABLE II. ANALYSIS OF ALLERGIC REACTION AND CLINICAL RESPONSE TO INHALED PROCAINE PENICILLIN MICROPOWDERS

Case Groups by Diagnosis	No. of Cases	No. Cases Prev. Treated with Penicillin	No. of Known Allergic Cases	No. Cases Prev. Sensitized to Penicillin	Allergic Reactions		Clinical Response		
					Local	General	Excellent	Good	Poor
No disease Volunteers	20	8	2	0	0	0	—	—	—
Acute Nasopharyngitis	48	28	6	2	0	2	22	16	10
Acute Trachebronchitis	33	25	13	4	(1) 2	(1)	15	16	2
Acute Sinusitis	10	8	3	0	0	0	8	1	1
Chronic Sinusitis	5	4	0	0	(1) 1	(1)	0	2	3
Acute Tonsillitis	5	1	0	0	0	0	4	1	0
Bacterial Pneumonia	4	2	0	0	0	0	3	1	0
Chronic Bronchitis and Bronchiectasis	6	4	0	0	0	0	3	2	1
Broncho Pulmonary Infection with Asthma	9	8	7	2	0	0	4	3	2
Misc. Respiratory Infection, e.g., Laryngitis and Cervical Adenitis	10	5	1	1	0	0	5	5	0
Totals	150	93	32	9	5	4	64	47	19

Note: Parenthesized numbers indicate that one person exhibited a local and a general reaction. Nine reactions occurred in seven individuals.

chronic infections and some acute infections which required more prolonged treatment. One individual received 300,000 units daily for one month by intranasal inhalation. Several patients with bronchiectasis have been given seven to fourteen day courses of procaine penicillin by inhalation during the past year. An attempt was made to treat common upper respiratory tract infections only when the manifestations were most frequently caused by the action of bacteria rather than during the early stages when symptoms were presumably of virus origin.

CLINICAL RESULTS AND INTERPRETATIONS

In general, this regime of procaine penicillin inhalation therapy has been found to be satisfactory clinically. Almost all of the patients voluntarily declared a preference for the procaine salt to similar micropowders of sodium penicillin. Several persons who discontinued therapy before completing the prescribed schedule obtained satisfactory clinical results. A rather surprising observation noted by 110 of the 150 cases was symptomatic relief of sore throat, nasal discomfort, and associated headache, almost immediately or within a few hours. Three pneumococcal pneumonia cases were treated successfully with this form of penicillin therapy. A fourth individual received an initial injection of 300,000 units of procaine penicillin in oil followed by a seven-day course of inhalation therapy at home and responded satisfactorily. Two patients with a diagnosis of chronic bronchitis failed to respond to intramuscular injections of penicillin in oil in adequate dosage but obtained lasting relief after inhalation therapy. An analysis of the clinical results and allergic reactions from inhaled procaine penicillin is shown in Table II.

The interpretation of the patient's responses to inhaled procaine penicillin, was based on clinical observations and evaluation in each case. The

criteria used included the following: the type and severity of the infection, the duration of symptoms prior to treatment, past history referable to similar episodes, their severity, usual duration and complications; plus the completeness and rapidity of recovery or sustained relief of signs and symptoms of the infection.

Response to therapy was classified as excellent, if all symptoms and signs were definitely improved within twelve to twenty-four hours followed by rapid recovery and no recurrences or complications. The clinical result was considered good if the same responses were obtained within twenty-four to seventy-two hours. The response was classified as poor if there were little or no shortening of the usual duration of the infection, incomplete relief of signs or symptoms, or if recurrences or complications appeared during or soon after completing a course of treatment.

Based on this classification, the intranasal inhalation of micropowdered procaine penicillin is considered an effective form of treatment for acute bacterial infections of the upper respiratory tract (130 to 150 cases). If the cases of acute nasopharyngitis and chronic sinusitis are excluded, the response is almost uniformly good (ninety of ninety-six cases). The ten failures among the forty-eight patients classified as having acute nasopharyngitis demonstrate that the manifestations frequently may be caused by organisms insusceptible to the action of penicillin. However, the observation that fifteen of these forty-eight patients obtained rapid relief and uncomplicated recoveries provides indirect evidence that penicillin sensitive bacteria are involved in the pathogenisis of these diseases.

CLINICAL ADVANTAGES OF PROCAINE PENICILLIN

Procaine penicillin micropowders are an improvement over similar sodium or potassium penicillin preparations since they are:

1. Less irritating to nasal and pharyngeal mucous membranes.
2. Less disagreeable in taste and odor, more pleasant to inhale, and tolerated by young children.
3. Less hygroscopic, and remain dry and dispersed, they require less time and effort to inhale.
4. Mildly anesthetic, they frequently give prompt symptomatic relief from nasal inflammatory processes.
5. Relatively insoluble, they remain in contact with mucous membranes longer, and provide continuous local antibiotic action.

REACTIONS TO INHALED PROCAINE PENICILLIN

The incidence of all allergic reactions has been seven cases in 150. Three known atopic individuals developed mild generalized urticarial reactions between the third and fifth days of treatment. There were no associated local reactions in the nose or throat. The fourth case had a pre-existing epidermophytosis of the hands and feet and developed an exacerbation of these lesions on the seventh day of treatment. This patient, a non-allergic

individual, had neither received penicillin nor experienced any reaction to procaine injections previously. He developed an allergic inflammation of the nasopharyngeal mucous membranes also, characterized by swelling and itching of the nasal passages and moderate infraorbital facial edema. The local and systemic manifestations persisted for approximately five days and were moderately well controlled by the oral administration of Neoantergan (200 mg. per day in divided doses). The fifth case, an atopic individual, developed an allergic nasal reaction similar to that seen in the fourth case. He also suffered an activation of his epidermophytosis but it was less severe and of shorter duration. Two other allergic persons developed local reactions. One sustained slight nasal congestion and the second a mild perioral edema which followed administration by oral inhalation. Both of these disturbances were considered to be penicillin sensitization reactions. These individuals had suffered other allergic disturbances previously from other allergens. Six of the seven persons exhibiting allergic reactions were known to be hypersensitive individuals.

DISCUSSION

The 4.6 per cent incidence of allergic reactions observed in this group is almost identical with that encountered following the inhalation of sodium or potassium penicillin micropowders. The procaine salt of penicillin appears to be no more allergenic than sodium penicillin in the purified crystalline state. This series, however, includes a larger proportion of individuals with allergic histories or definite manifestations of allergy (thirty-two in 150) than is encountered in the general population. Ninety-three of these people are known to have received penicillin by inhalation or intramuscular injection in the recent past. A few of these individuals may have been sensitized to penicillin unknowingly. Therefore, the 4.6 per cent reaction incidence observed in these 150 patients indicates that procaine penicillin is probably less allergenic and may produce fewer reactions than reported (4.9 per cent) in our larger sodium and potassium penicillin series[5,26,27,28] and by Krasno et al (3 to 6 per cent), who used sodium penicillin dust.[16,17,18]

Procaine therapy by intravenous injection has been shown to alleviate allergic reactions caused by foreign serum and other allergens and has been reported to be a useful drug for various manifestations by hypersensitivity.[1,7,21] Therefore, this action may be responsible in part for the apparent reduction in antigenicity of penicillin when it is combined chemically with procaine. It is also possible that a decreased rate of absorption favors the development of fewer sensitizations.[9] Another plausible explanation for the relatively lower incidence of local allergic reactions (five in 150) is that comparatively few persons have been locally sensitized to the procaine penicillin salt. In addition, it has been reported by Haley et al[10] that one of the important mechanisms of local action of various antihistaminic agents is vasoconstriction. Capillary constriction may be a sig-

nificant factor in the pathogenesis of mucosal sensitization. It could assist in decreasing the rate and amount of procaine penicillin absorption from the respiratory membranes.

The authors are not aware of studies pertaining to the fate of procaine penicillin in body tissues. The unaltered incidence of systemic allergic reactions noted during this investigation (four in 150) indicates that penicillin probably dissociates from the procaine salt in body tissues and then acts in its usual manner regarding its sensitizing properties.

SUMMARY

The intranasal inhalation of micropulverized procaine penicillin G in 100,000 unit doses two or three times daily, has been found to be an improvement over sodium or potassium penicillin micropowders when administered for similar purposes.

There has been no increase in the incidence of allergic reactions over that observed following the inhalation of sodium or potassium penicillin dusts. The chemical combination of procaine with penicillin reduces the local anesthetic activity of procaine and possibly alters the local antigenicity of penicillin while it remains chemically combined. No reactions attributable solely to procaine have occurred. Atopic individuals and patients sensitized by previous penicillin or procaine administration should not be treated with procaine penicillin salts indiscriminately because they are prone to develop allergic manifestations.

ACKNOWLEDGMENTS

The authors are grateful to:

1. The Lederle Laboratories, Division of American Cyanamid Company, for a grant-in-aid which supported this investigation and for generous supplies of procaine penicillin micropowders and the inhalators (trade mark, "Penlators").

2. Miss Sofie Mezzio and Mrs. Clara Keskinen, for assistance in collecting completed case reports from ward physicians and for secretarial assistance during the preparation of the bibliography.

3. Mrs. Rose B. Lederer, for valuable aid in the collection of samples for antibiotic assay and for secretarial assistance in the preparation and editing of the manuscript.

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Plan now to attend the Seventh Annual Congress of The American College of Allergists February 11-14, 1951, to be held at the Edgewater Beach Hotel, Chicago.

EXTREME SENSITIVITY TEST REACTIONS TO SILK IN A NEGATIVE SKIN-TEST POLLEN PATIENT

A Clinical Study

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MISS C. L. R., aged twenty-eight, a secretary, was referred by Dr. C. J. Boehs, an otolaryngologist, and first seen on June 20, 1944. She has been under observation in our office ever since, in all some five years. The reference diagnosis was vasomotor rhinitis of considerable severity, without other nasal abnormalities, of three years' duration. According to the patient, the symptoms seemed a little less severe during the summer months of the first year of her trouble, but for the past two years the nose had never been clear except for a few hours at a time when under medication for the purpose. It was later shown that such local nose medication had no bearing on the case. The symptoms were worse at night, perennial in character and without seasonal variations. There were no known clinical food sensitivities; and, while under our care, foods were shown not to be important.

DIAGNOSTIC SKIN TESTS

Dermal: Pollen, foods, cottonseed, flaxseed: all negative. Wool, horse and cat hair: slight + positive. Silk: ++++.

Intradermal: Pollens—1:500 dilutions: negative. Fungi—1:400 dilutions; negative. House dust—1:5000: ++. Foods—Negative except +++ to tomato, of no clinical significance. Silk (later, January 5, 1945) 1:50,000: ++++++. January 29, 1945 1:5,000,000: +++.

The silk extracts used were dilutions of a standard Lederle silk extract for intradermal testing. The undiluted material was used for scratch tests.

This same extract has been included for many years in our routine dermal testing set, and in its use in over a thousand cases we have seen only one or two strong positive reactions. This case showed no dermal lesions—the usual clinical response to silk allergy, and there was no discoverable silk contact. There was no known contact with animal dander.

In view of the perennial symptomatology and the nocturnal increase of symptoms, this case was rather naturally classified as one of silk, house dust, and bedding etiology; the usual precautions of avoidance of such contacts were instituted, including impervious, dust proof pillow and mattress covers. The patient's story of improvement in summer the first year of trouble added to the probability of this diagnosis. Subsequent events lead to doubts of the correctness of her observations on this point.

TREATMENT

1. The silk dermal test was done weekly as a therapeutic measure eight times, always with the usual ++++ reaction. Later this was changed to 0.01 or 0.02 c.c. of a 1:5,000,000 dilution of this standard silk test extract. Eleven of such treatments were given, always with a +++ or ++++ local reaction.
2. Coseasonal intradermal treatment of our current spring and summer pollens, timothy for our grasses, carelessweed, and mesquite, using 0.01 or 0.02 c.c. of the 1:500 dilution and, later, the usual preseasonal subcutaneous treatment with a mixture of equal parts of these pollens.
3. Preseasonal subcutaneous ragweed, and, later, coseasonal intradermal treatments, using 0.01 or 0.02 c.c. of the 1:500 dilution.
4. The same for our midwinter cedar season.
5. Ascending doses of house dust.

There was absolutely no diagnostic justification for the use of pollen in this case. It was included in the treatment merely as a possible accessory secondary factor, as negative skin-tests pollen cases often complicate cases in our community definitely sensitive clinically to other positive skin test factors.

In view of the fact that ascending doses of pollen given with the house dust produced only minimal local reactions, and no obvious systemic disturbances, such minimal local reactions were disregarded, and dosage increases continued in the same manner. During this period we regarded this case still merely as one of house dust etiology difficult to desensitize.

The first evidence of pollen being a factor in this case occurred on February 1, 1945, when 0.16 c.c. of the 1:10 dilution of the timothy, carelessweed and mesquite mixture used as preseasonal subcutaneous treatment gave a ++++ delayed local induration. Ten days later, one-half this dose gave an immediate +++ local reaction. Doses were at once reduced to the non-reacting 1:50 dilution. There was little or no improvement during all this time.

In May 1946, after a year of handling, or, more correctly speaking, of mishandling, our eyes were finally opened to the air-borne pollen factors in this case with definite clinical proof. During that month, the patient took advantage of a two and one-half weeks' vacation, to embark on a bus tour to the City of Mexico. Here in San Antonio, at her departure, the nasal symptoms were of the usual severity, but they cleared at once on reaching the City of Mexico three days later, and they continued clear during the entire stay there. This symptom-clearing was of decided significance for two reasons:

1. Mexico City is practically free of antigenic air-borne pollen at that time of year.
2. Her house dust contact in Mexico City was far greater than in her local San Antonio environment.

The clearing of symptoms under these conditions practically eliminated these house dust and silk factors as being of clinical importance. Further definite confirmation of the pollen influence in this case was seen from subsequent events. The last 300 miles of the 800 mile return bus trip, especially the last 150 miles, brought the patient into contact with roadside and field pollen. She had no more than reached the beginning of this last 150 mile point at the Texas-Mexico border when nasal blockage and severe catarrhal symptoms immediately recurred, persisting for months. We had therefore definite confirmation of pollen or pollen and fungus etiology and could rule out silk and house dust.

From this point on, this case was considered correctly, as one requiring appropriate pollen treatment and correct pollen dosage. After going over our initial pollen doses, it was decided that our patient was actually more sensitive than we had thought, and needed more attention paid to minimal local reactions and post-treatment symptom exacerbations.

With our midwinter cedar, spring trees, grasses, carelessweeds, mesquite and fall ragweeds, we have some five successive pollen seasons in San Antonio and in some years we have antigenic atmospheric pollen continuously present from early or mid-December to the middle or end of November. Positive skin test cases are seen embracing several and, at times, all of these seasons. In addition, negative skin test pollen cases, especially of the low degree of sensitivity type, are not particularly rare in our community, both the uniseasonal and multiseasonal types, and occur with or without positive skin tests to other antigens both relevant and irrelevant. Local conditions probably account for the appreciable percentage of negative skin test pollen cases seen in our community. In the absence of any single perennial pollination factor, such perennial symptomatology in our opinion necessitated the inclusion of all the important pollens of at least four of our important pollen seasons extending from mid-December to the middle or end of November, because we often

have years in San Antonio with only three or four weeks of freedom from atmospheric antigenic pollen. This state of affairs requires multiple injections and concurrent preseasonal, coseasonal and perennial treatments at each visit in a patient having symptoms, and presenting at most visits a problem of differential diagnosis between underdosage, overdosage and the possible omission of some current airborne pollen. Obviously the handling of all cases of this type is difficult. As a matter of fact, it required one and one-half to two years of weekly visits in this particular instance to secure any improvement. In November, 1946, fungi were added, again empirically, in spite of negative skin tests.

Following her return from Mexico this case was treated perennially with five separate injections.

1. Ragweed.
2. A mixture of equal parts of oak, hackberry and pecan.
3. A mixture of equal parts of timothy, carelessweed and mesquite.
4. A mixture of equal parts of Alternaria and Hormodendrum.
5. Cedar.

In addition, booster coseasonal intradermal pollen treatments were given as needed; only pecan, with a pollination season of only a few weeks in the spring, gave any appreciable local reaction. For the last eight months, there has been no vasomotor rhinitis and almost none for four months previous. A ++++ scratch test to silk is still present. Also, the patient continues to work in the same office and lives in the same environment. If she had been sent to the Texas seacoast when first seen, the pollen etiology would, in all probability, have been established immediately. Direct intranasal or ocular pollen applications might also have been given in earlier confirmation. After the clinical demonstration, there was no particular advantage in applying these testing methods.

The patient toured Europe from mid-July to mid-September, 1949, with no nasal symptoms, although no precautions were taken against silk or house dust.

No attempt is being made to account for the extreme variation between the highly positive skin tests to silk and the negative pollen-fungi tests that were actually the basis of the symptoms. However, with an individual employed in or contemplating employment in a silk mill, this silk reaction would undoubtedly have been a decided clinical significance which was completely lacking in this instance.

SUMMARY

The case history is reported for a patient exquisitely sensitive dermally and intradermally to silk and with negative intradermal tests to pollen and fungi. She was shown clinically to be a pollen and possible fungus case, and not at all sensitive to silk.

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Keep up with the newest developments in the treatment of allergy by attending the Graduate Instructional Course sponsored by The American College of Allergists at the Edgewater Beach Hotel in Chicago, February 9-11, 1951.

IMPOTENCE—AN UNUSUAL SIDE REACTION IN ANTIHISTAMINIC THERAPY

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NUMEROUS reports have appeared in the literature concerning the occurrence of side reactions in the use of the antihistaminics. Drowsiness, dizziness, nervousness, palpitation, headaches, nausea, diarrhea, weakness and dryness of the mouth were the allergic manifestations most commonly noted. Others reported of less frequent occurrence have been abdominal pain, bleeding from the rectum and premature menses.

A rather unusual side effect has been found by the author in two cases—that of impotence. In the first case, Pyribenzamine was the drug used; in the second, Pyribenzamine and Thephorin.

Case 1.—This patient was a twenty-six-year-old white laborer, who came to my office in June, 1947, with a history of urticaria of ten days' duration. Pyribenzamine, 50 milligrams three times daily, had been prescribed by his family physician, and it gave him some temporary relief from the itching. However, he complained that on the fourth day of Pyribenzamine therapy, he developed sexual impotence. This he considered worse than the urticaria itself, since he had been married only three months. On discontinuance of the Pyribenzamine, he was able to have normal erections; the urticaria became worse. However on elimination of several offending foods, the urticaria cleared up.

Case 2.—The second patient was a forty-three-year-old white male clerical worker who was first seen by the author on June 9, 1948. He gave a history of itching with welt formation, which began a year previously and had become worse during the past six weeks. Bathing aggravated his symptoms. The patient had a long past history of terminal ileitis of seventeen years' duration, during which period he had had four major operations, the last in 1946. His referring physician had given him Pyribenzamine, 50 milligrams four times daily, in May, 1948, which, as he put it, "knocked me out." In addition, it caused sexual impotence. After he stopped this medication, the impotence cleared up. His medication was changed to Benadryl, which in 50 milligram dosage caused drowsiness but not any sexual changes. During the course of study, I prescribed Thephorin, 50 milligrams three times daily, which after administration for four days produced impotence. Virility returned again after Thephorin had been discontinued for two days. The impotence had not returned in two months. He is taking no antihistaminics.

COMMENT

Two cases are reported of sexual impotence in male following administration of antihistaminics. In the both cases, Pyribenzamine, an ethylenediamine derivative, caused this unusual side reaction. In addition, in the second case, Thephorin, which is chemically unrelated to Pyribenzamine and has no related sedative action, also produced sexual impotence. Benadryl, a drug closely related to Pyribenzamine, did not cause this in the second patient.

In both cases, the impotence cleared up with immediate discontinuance of the drugs, though the allergic condition either became worse or continued unabated. No relation existed between the loss of virility and the primary allergic condition.

135 West Main Street

Progress in Allergy

ANTIHISTAMINIC AGENTS
A Review

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Boston, Massachusetts

(Continued from the March-April issue.)

The varying reports of the response of patients with bronchial asthma to antihistamine drugs lead to a number of studies. In four asthmatic patients treated by Walton and Kristjanssen-MacDonnell,[169] the drug intensified symptoms. In the series by Guchs et al[170] all of the thirty patients presented a long history of bronchial asthma resistant to the usual measures. In twenty-eight there was demonstrable organic disease of the sinuses, lungs or heart. In eleven there were no skin tests and in nineteen there were skin sensitivities and chronic infection. The patients were observed for six months, while taking up to 500 mg. daily. Seven patients reported symptomatic relief, of whom two obtained similar relief with a placebo. All of these were free from organic, heart or lung disease. Twenty-three patients reported no relief. In all of these, secondary pathological lesions were present, but Benadryl appeared, however, to enhance the effect of the antispasmodic drugs added when the Benadryl alone was found to be ineffective. The drug had no effect on severe asthmatic attacks. In only three patients were the side effects sufficiently severe to warrant discontinuing treatment, although 93 per cent of the patients presented some side reactions. In the series by Rubitsky et al[171] there were fifteen acutely ill asthmatic patients, eight of whom were intractable. Benadryl or Pyribenzamine was administered by rectal, aerosol and intravenous routes, the doses ranging from 20 to 50 mg. intravenously given at a rate of not more than 10 mg./minute. Once the severe bronchospasm was relieved, the patients were maintained with Pyribenzamine, 2.5 per cent, solution by aerosol alone, or mixed in equal parts with a bronchodilating drug. Ten of the fifteen patients obtained significant relief, or restoration of epinephrine sensitivity. The side reactions, however, included drowsiness, dizziness, headache, transient chilliness, nausea and fatigue. In one patient the vital capacity increased from 1300 to 2300 c.c. Six inhalations of Isuprel aerosol increased the vital capacity an additional 500 c.c. The best results were obtained in those patients who had previously been found to be histamine-sensitive. The duration of relief with the aerosol method was three to four hours and with the intravenous route, six hours. The oral medication brought on relief in sixty to ninety minutes and the rectal medication in fifteen to thirty minutes. Confirmatory results were reported by Friedman[172] who treated twelve patients with Benadryl aerosol solution, to which penicillin or other antibiotics were added when indicated by the presence of infection. Nine of the patients had previously been treated with various systemic antihistamine preparations, only two receiving benefit. Prophylactic administration of Benadryl aerosol prevented acute attacks or increased the intervals between attacks, decreasing their severity. None of the patients developed resistance to the drug, but two patients required increased doses after prolonged administration. In only two patients were there side reactions as marked by headache. One additional patient suffered from a dry mouth.

Spirometric studies in sixteen patients with extrinsic bronchial asthma given

Benadryl, 100 mg. orally shortly after the onset of a moderately acute attack of asthma showed no changes in vital capacity, tidal air, minute ventilation, expiratory differential, respiratory rate or degree of emphysema as noted by Levy and Seabury.[173] Six patients stated that there was complete relief of their dyspnea; five of the sixteen patients subsequently given ephedrine and aminophylline showed an increase in vital capacity, tidal air, minute ventilation and respiratory differential. There was, however, no increase in respiratory rate. No marked effect was seen in one patient with emphysema. The side reactions are described as vertigo, dry mouth, drowsiness, anxiety, weakness, epigastric pain, nausea, difficulty in co-ordination, feeling of mild inebriation, blurred vision, tinnitus, extreme dyspnea, palpitations, and it should be noted, precipitation of status asthmaticus. The drugs may act intravenously when not effective orally as shown in the report of Goldman.[174] All of his fourteen patients had not responded to Benadryl. In nine cases of urticaria there was immediate improvement, disappearance of swelling and alleviation of symptoms. One case of contact dermatitis was relieved from itching, partially, and in a second case, quickly. There was little effect in three cases of asthma. The dose most commonly employed was 10 mg. four hourly, the schedule being employed in one instance as long as twenty days, no patients demonstrating toxic effects.

Of 100 patients given Benadryl orally by Barksdale and Hall,[175] twenty-two of twenty-five patients with poison ivy and ten of twelve with chronic urticaria, as well as fourteen with acute urticaria of unknown origin, two of fifteen with atopic dermatitis, and three patients with hay fever were relieved. Benadryl was useful in the urticaria due to penicillin and effective as well in that due to streptomycin, trichophytin, merthiolate and sea food sensitivity. Patients, however, with dermatographia, erythema multiforme, scabies, psoriasis or idiopathic pruritus were not relieved. In six patients it was necessary to discontinue the use of the drug because of the unpleasant side reactions, which included those usually described and, in addition, "contractures of the arms and legs." In two patients with hay fever there were withdrawal symptoms as demonstrated by nausea.

As soon as new antihistaminic agents began to make their appearance, comparisons between them were in order. In this regard, one of the best papers is that by Loveless and Brown[176] who used Benadryl in fifty-three patients and Pyribenzamine in 150, the dose being 50 mg. orally repeated in one to four hours if necessary, but not more often than five times in any twenty-four hours. Constitutional reactions following overdosage with therapeutic allergens responded best, and then in decreasing order, acute urticaria, chronic urticaria, extrinsic allergic rhinitis and drug eruptions. In twenty patients with extrinsic and intrinsic bronchial asthma, only half responded, the improvement being partial, only a third of the intrinsic patients reacting at all. Atopic dermatitis was least responsive. Both drugs were given to thirty-three individuals, twenty-three of whom observed no difference, while in the remainder half preferred one drug and half preferred the other, but proportionately more patients had toxic effects from Benadryl than with Pyribenzamine, the most frequent being drowsiness, mental sluggishness, and gastrointestinal disturbance occurring in 61 per cent of the patients given the former, and in only 20 per cent of those given the latter. Other infrequent reactions were exhaustion, excitement, and dizziness. In a second report, Loveless[177] analyzed her own 200 patients and an additional 3600 taken from the literature. Sedation was the most common side effect following the administration of Benadryl, additional symptoms being drowsiness, inability to concentrate, mental confusion, prolonged and untimely sleep, stupor and narcolepsy. Three times as many reactions occurred with Benadryl as with Pyribenzamine, of which the most common side effects were in the gastrointestinal tract, as nausea, bad taste, anorexia, pyrosis, epigastric distress, indigestion, abdominal cramps and occasional vomiting and diarrhea. With Benadryl, some patients had wakeful excitement and others, insomnia; some, sedation, and others, irritability and nerv-

ous tension. Common to both drugs was dizziness and vertigo, occurring in 7 per cent of those taking Benadryl and 1 per cent of those taking Pyribenzamine. The gastrointestinal symptoms occurred in 8 per cent of both groups, but in all, 46 per cent of the patients given Benadryl manifested sedation, and only 8.5 per cent of those taking Pyribenzamine. As regards the conditions treated, 75 per cent of the patients with non-seasonal rhinitis and hay fever showed improvement, which occurred in a little over half the patients with intrinsic allergic rhinitis and less than half of those with bronchial asthma, the response being least satisfactory in those with non-seasonal extrinsic bronchial asthma. Acute and chronic urticaria responded well in 80 to 95 per cent of the cases, with improvement seen in 60 per cent of those with atopic dermatitis. In a small group of cases including eczematous dermatitis and miscellaneous skin conditions, there was only 45 per cent improvement, with pruritus being relieved in 16 to 20 per cent of the cases. Application of the X^2 Test of the author's figures shows the difference is significant in the cases suffering from intrinsic bronchial asthma only, but in any case, the analyzed figures show undesirable reactions, as noted in 61 per cent of 655 trials with Benadryl and in 21 per cent of 1905 trials with Pyribenzamine. Sedation was undoubtedly five times more common with Benadryl.

Kierland and Potter[178] administered Benadryl, Pyribenzamine and also Thenylene to 126 patients suffering from a number of allergic conditions, none receiving more than one drug at a time. It was felt that no statistically valid conclusions could be drawn, since different physicians administered the drugs. Drowsiness was most marked after the use of Benadryl, but also occurred with patients taking Thenylene. The clinical comparisons showed a high degree of similarity of results with the three drugs. Similarly, Blumenthal[179] used Benadryl, Pyribenzamine and Histadyl in 108 patients with hay fever. Of those treated with hyposensitization alone, good results were obtained respectively in sixty patients, appreciable results in thirty-two, and none in sixteen. An additional 108 patients treated with hyposensitization and the drugs reported corresponding relief in eighty-eight, twelve and eight. In sixty-two patients given 50 to 100 mg. Benadryl as needed, corresponding figures for good results were twenty-eight; for appreciable results, twelve; and for none, twenty-two. In fifty-five patients given Pyribenzamine, the figures were twenty-two, sixteen and seventeen; and for twenty-two given Histadyl, seven, eight and seven. No conclusions, therefore, could be drawn as to the efficacy of any of the drugs, although the best results were obtained with hyposensitization and a drug, compared to either injection or drug therapy alone. Bernstein[180] compared Benadryl, Pyribenzamine and Neo-Antergan and found the second to be the most effective with the greatest number of toxic reactions following Benadryl. Neo-Antergan apparently fell between the two. Alperstein[181] chose patients who had experienced toxic reactions with Benadryl and Pyribenzamine and administered, instead, Chlorothen (Tagathen) and Bromothen. In all of twenty-six individuals, there was relief in fifteen to thirty minutes and no toxic reactions. The 50 mg. dose given three times a day alleviated all symptoms after one day of therapy in six, and after two to six days in the remainder. In an additional forty-seven patients suffering from pruritus, rhinitis, urticaria and eczema, who had neither received Benadryl nor Pyribenzamine, twenty-five were given Chlorothen and twenty-two Bromothen, with complete alleviation of symptoms and no toxic reactions.

Waldbott and Gadbaw[182] compared Benadryl, Decapryn, Hydryllin (Benadryl and aminophylline), Phenergan and Pyribenzamine. In addition, some patients received Isuprel aerosol and Amphaphrene. Neo-Antergan and Trimeton were also administered; the side effects were listed as occurring in 61 per cent of the patients taking sublingual Isuprel and for the antihistaminic agents, 56 per cent of those taking Benadryl, 48 per cent for Decapryn, 42 per cent for Trimeton and 1 per cent for Phenergan. The other drugs produced side effects in 15 to 38 per cent of the patients.

In some cases there was temporary aggravation of the allergic symptoms. Serial blood counts and urine examinations indicated no unusual changes. The numbers of patients studied, however, did not lend themselves to statistical analysis. This is equally true for the paper by Harris[183] on the use of Benadryl, Histadyl, Hydryllin, Pyribenzamine and Compound 1695, sixty-five patients being treated successively with the drugs listed. In this group, it appears that Histadyl and Pyribenzamine were slightly more effective than Hydryllin and Benadryl, although the former was more effective in the cases of bronchial asthma associated with pollinosis. Compound 1695 was not as effective as the others. Although almost all the reports on animal experiments are purposely omitted from this clinical review, nevertheless, a paper by Winter[184] comparing the effects of Benadryl, Hetramine, Neo-Antergan, Phenergan, Pyribenzamine, and Compound RP 3015 on guinea pigs is worthy of study. After large doses (10 mg./kg.) of the drugs listed, the animals survived a thousand times or more of the usual lethal doses of histamine, although many of them died in a few hours of perforating gastric ulcer, presumably induced by the histamine. In a second experiment, varying doses of one of the drugs or of Pyribenzamine, Benadryl or Hetramine were injected thirty minutes before the intravenous injection of histamine dihydrochloride, 0.5 mg./kg. All of the controls died within a few minutes following histamine injection. The drugs could be listed in decreasing order of potency as Neo-Antergan, Pyribenzamine, RP 3015, Phenergan, Benadryl and Hetramine. The same order of potency was substantially established when the drugs were administered to guinea pigs who had been exposed to histamine aerosol as also in experiments with isolated intestinal strips. In acute toxicity experiments, none of the drugs was highly toxic, in doses comparable to the therapeutic dosage levels, but delayed deaths occurred, sometimes a week after a single injection in the case of Phenergan and Benadryl. The side reactions were most violent after Phenergan and least noticeable after Neo-Antergan, although RP 3015, Phenergan and Benadryl have a lower acute toxicity than Neo-Antergan, the ratio of the toxic to the effective dose being highest for this drug, the clinical qualities of which will be described below.

DECAPRYN

The animal experiments for Decapryn succinate were very competently performed by Brown and Werner,[185] who found it low in toxicity and a potent antagonistic agent for the bronchoconstriction, resulting from the intravenous injection of histamine in guinea pigs, antagonizing up to 200 and in some cases, 320, lethal doses of histamine. In a second communication[186] death from anaphylactic shock did not result in eight guinea pigs passively sensitized by injections of antibeef serum (1.0 c.c.). Toxicity studies by Thompson and Werner[187] showed that no chronic toxicity occurred in dogs given Decapryn succinate several times a day over a period of two months. Further studies by Snyder et al[188] showed that in rats, in the first twenty-four hours following intravenous administration of Decapryn (25 mg./kg.), 8 to 17 per cent was excreted in the urine.

The clinical evaluation by Brown et al[189] showed that small doses (6.25 to 150 mg.) four times daily gave excellent relief to sixty-two of 123 allergic patients suffering from bronchial asthma, urticaria, angioneurotic edema, atopic eczema, migraine, generalized pruritus, erythema multiforme, contact dermatitis, prurigo, and vasomotor, infectious or allergic coryza. The response was moderate in thirty-six patients, negligible in twenty-five. The majority of patients received single doses (12:5 to 25 mg.) with complete relief being experienced by 80 per cent of the patients with typical hay fever, and 85 per cent of those with urticaria and angioneurotic edema. Marked relief was obtained by 30 per cent of fifty-four patients with bronchial asthma, with moderate relief in 40 per cent of the patients, who nevertheless required larger doses. Of the twenty-three patients who experienced side reactions,

fifteen were in the asthma group, with reactions being moderate in five of the remaining patients and severe in three. The most common complaint was drowsiness.

Feinberg and Bernstein[190] found the drug highly effective in inhibiting the wheal and flare reaction to histamine in man, doses of 12.5 to 50 mg. relieving sixty-two of eighty-one patients with hay fever, nineteen of thirty-four with non-seasonal vasomotor coryza, five of six with dermatographism, and relief of some of the swelling and itching of urticaria and angioneurotic edema in six of nine. None of twenty-seven patients with bronchial asthma associated with hay fever were affected. Side reactions occurred in thirty-nine patients with sedation and sleepiness in thirty-six, nervousness in four, vertigo in four and headache in two, with epigastric pain in one. In six months' use of the drug, no serious effects were noted.

Further studies by MacQuiddy[191] on forty-three patients with hay fever treated with Decapryn, 12.5 mg., preceding breakfast and lunch, and 25 mg. before retiring, for one to thirty-three weeks, gave good results in nineteen patients; fair for eight and poor for sixteen, with ten patients reporting drowsiness and/or nausea. Of thirteen patients treated in the same manner for asthma and hay fever, the results were good in eight, fair for four and poor for one. Of fourteen patients with asthma alone treated similarly, the results were good for four, fair for seven and poor for three, with one in each group reporting drowsiness. Of thirty-three patients with vasomotor rhinitis only, results were good for twenty-two, fair for five, and poor for six, with two reporting drowsiness. Of ten patients with urticaria, results were good for seven and poor for three, with one with drowsiness. In ten patients with migraine, good results were seen in five, fair for one and poor for four, with three feeling nervous or drowsy. Two patients of five with eczema reported good results, with fair for two and poor for one, with one reporting drowsiness. Three patients with ocular allergy reported good results for two and fair for one.

Using Decapryn as one of nine antihistaminic agents in the treatment of pollinosis, Maietta[192] found that one of three suffered drowsiness, although four of five receiving Pyribenzamine suffered drowsiness and nausea, and four of five receiving Benadryl presented the same complaint. This was equally true of four of five patients on Histadyl and five of fourteen on Thephorin, with three of six on Neo-Antergan and all of three on Tagathen. One patient taking Decapryn had numbness, and two on Histadyl complained of fatigue and insomnia.

The Council on Pharmacy for the A.M.A.[193] recommends the dosage of 12.5 mg. be given initially for adults, with subsequent average doses of 25 mg. or more as needed. The drug is recommended as a highly effective antihistaminic agent, but is listed as having a high index of sedation which sometimes precludes its use, particularly when large doses are required.

DIATRIN

Ercoli et al[194] described the toxicologic and antihistaminic properties of Diatrin, a relative newcomer to the field in June of 1948. The usual laboratory studies showed that the subcutaneous administration of 0.5-0.50 mg./kg. gave protection against 100 lethal doses, but did not prevent gastric ulceration which followed in five to eighteen hours. Subcutaneous or intravenous administration of 0.05 mg./kg. protected animals against lethal histamine asthma and 0.5 mg./kg. intravenously reduced or blocked histamine-induced hypotension in dogs for more than two hours. The intravenous LD_{50} for rabbits and guinea pigs was 30 mg./kg. The pharmacology of the compound is similar to that of other antihistamine drugs. In a later communication, Chessin and Ercoli[195] showed that of 800 guinea pigs sensitized with two injections of horse serum, 0.1 c.c., given subcutaneously or intraperitoneally forty-eight hours apart, those who after eighteen days were re-injected intravenously with serum, 0.5 c.c., after protection with Diatrin, 5-10 mg./kg., survived, while 80 to 85 per cent of the control guinea pigs died in anaphylactic shock. Antergan, Benadryl,

Neo-Antergan and Pyribenzamine gave similar results. Animals injected one day later went into fatal shock, the anaphylactic reaction lasting for the same length of time as the presence of the drug in the organism.

The clinical studies by Combes et al[196] concern eighty patients treated with Diatrin, 100 to 1,000 mg. daily, in the form of plain and enteric-coated tablets. All of nine with urticaria, two of three with neurodermatitis, three of thirty with dermatitis venenata, two of four with miscellaneous dermatoses, and one of five with penicillin urticaria, one of three with dermatitis medicamentosa, one of ten with atopic eczema, one of three with erythema multiforme, and one of nine with recurrent vesicular eruptions were completely relieved of their symptoms. Forty-three patients were not relieved, while seven obtained slight and nine moderate relief. In all, seven patients presented minor side effects, including nausea, vomiting, diarrhea, urinary frequency, and generalized burning of the skin. In only three instances was the drug discontinued because of side reactions, which were not present in those patients who received the enteric-coated tablets. In a study Kugelmass[197] used Diatrin and also Benadryl and Pyribenzamine; seventeen of fifty-one infants and children with gastrointestinal allergy being treated with the three drugs. Diatrin and Pyribenzamine improved the symptoms of vomiting 35 per cent, the colic, 50 per cent, and the diarrhea, 25 per cent. Benadryl was less effective. Diatrin relieved 75 to 90 per cent of the rhinorrhea, sneezing, nasal itching and nasal symptoms of 19 patients, while Benadryl relieved 65 to 85 per cent and Pyribenzamine, 70 to 88 per cent. In the treatment of seventy-two patients with vasomotor rhinitis, Diatrin was slightly more effective than the other two drugs, but at the best the patients achieved only 45 to 60 per cent relief. Each of the three drugs is reported as being effective in "primary hereditary bronchial asthma," and occasionally effective in secondary acquired asthma, while ineffective in the residual lung injury type. Diatrin was reported as the least toxic of the three drugs. Drowsiness occurred in 30 per cent of those treated with Benadryl, 22 per cent of those treated with Pyribenzamine, and 18 per cent of those treated with Diatrin. Other toxic reactions include irritability, digestive and skin disorders.

DIPARCOL

Another new antihistaminic agent, originally known as RP 2987, and used chiefly in Europe as Diparcol, has been reported upon by Gray[198] as improving two post-encephalitic and one senile vascular case of Parkinsonism, the patient being controlled by alternation of Diparcol and Solanaceus alkoloids. One of the patients, who was helpless and bedridden, became active after six days, maintaining her improvement for several months. Two other post-encephalitic patients, two senile vascular Parkinson patients, one patient with a head injury and one with cerebral glioma at autopsy showed no significant response. The only side effect was mental depression, for which amphetamine is recommended. Meyer and Weissenbach[199] reported the drug as useful in eight women with acne rosacea, who manifested a paroxysmal facial erythrosis after eating. The dose was three to seven 50 mg. tablets daily; after three to four days of treatment the congestion disappeared, and after ten days, the therapeutic effect of the drug lasted for several days or weeks. Its action facilitated other means of therapy. An interesting facet in the studies of antihistaminic agents is furnished by the work of Mahaux and Kowalewski,[200] who administered 250 mg. of Diparcol to six patients with senile Parkinsonism and to nine patients with post encephalitic Parkinsonism and discovered that the basal metabolic rate was reduced from plus 39 to plus 15.5 in the first group, and from plus 49 to plus 11 in the second group. Extending the experiment to severely hyperthyroid patients, it was discovered that the basal metabolic rate was reduced from plus 46 to plus 14.4 in seven patients and from plus 24.5 to plus 7.7 in seventeen moderately hyperthyroid subjects, with a reduction from plus 15.9 to 2.6 in sixteen slightly hyperthyroid individuals. In normathyroid subjects, the reduction was from plus 4.9 to minus 1.4. In ten subjects with an

average basal metabolic rate of plus 29, exercise increased the rate to plus 51.8. After 250 mg. of Diparcol, and forty-five minutes of rest, the rate was plus 15.1. At this time, a second period of exercise equal to the first increased the rate only to plus 23.3.

DRAMAMINE

Although Dramamine has antihistaminic effects, the accidental discovery that it relieved motion sickness sent explorations in the field of antihistamine therapy in a new direction. Strickland and Hahn[201] reported in April of 1949 that eighteen individuals subjected to twelve one-hour flights at 5,000 ft., conducted so as to simulate flying intermittently through moderately turbulent air 75 per cent of the time, were not air sick in seventy-seven of 108 individual flights, as compared with forty-eight of 108 flights in which placebos had been given. The Dramamine, 100 mg., was administered prophylactically. Gay and Carliner[202] reported that Dramamine, 100 mg., followed by the same oral dose every five hours and at bedtime to a group of soldiers prior to a ten-day voyage prevented seasickness in all but two of 134 and that the oral administration to 389 during the ten-day voyage, two to twelve hours after the onset of symptoms, completely relieved 372 within one hour following the first dose. Seventeen subjects were only partially benefited or not at all. The incidence of severe seasickness affected 195 of 881 other soldiers, 187 of whom were completely relieved within thirty minutes. The substitution of placebos for the drug when it had been effective brought a return of symptoms. No side effects were noted. This paper has been commented upon at length by Tyler,[203] who points out that Drs. Carliner and Gay left themselves without adequate controls and that it cannot be determined with certainty from their paper to what extent the remission of symptoms was due to medication, change in weather, and sea conditions or to the phenomenon of adaptation. Tyler feels that on the basis of the single experiment reported upon, no convincing evidence has been presented to indicate that Dramamine is any more effective than hyoscine, 0.6 mg., in preventing motion sickness. This is further borne out by the paper by Strickland and Hahn (quoted by Tyler) in which it is reported that 55.6 per cent of the placebo group became sick. Under this moderately high sickness rate, 28.7 per cent of a like number receiving Dramamine became sick, indicating that the medication gave protection to about 50 per cent of the patients. Strickland[204] administered Dramamine to 206 young air force men not conditioned to flight. Of these, eighteen showed dizziness, mental depression or drowsiness. Strickland, however, reports that Dramamine is an effective preventive of motion sickness.

It is only natural that Dramamine would be used for other conditions associated with nausea and vomiting. Carliner et al[205] described its use in forty-three women to control the nausea and vomiting due to pregnancy. Of these, thirty-one were completely relieved within three hours. When a placebo was substituted, ten patients relapsed to recover when Dramamine was given. No relief was obtained in twelve patients.

Witzman[206] reported Dramamine, 300 mg. daily, as effective in forty-three of forty-seven patients, whose chief complaint was vertigo. Two additional patients showed marked improvement and two were not helped. Some patients complained of drowsiness necessitating the reduction of the drug to 25 to 50 mg. three to four times daily. The patients who suffered from vomiting were given the drug rectally by means of a perforated capsule. One patient with a suppurative labyrinthitis secondary to cholesteatoma and a second patient with early meningitis, secondary to chronic purulent otitis media with a fistula of the horizontal canal were completely relieved of their symptoms with Dramamine therapy.

It was soon discovered that Dramamine was effective also in relieving the vestibular reactions following labyrinthine fenestration operations. Campbell[207] administered the

drug (200 mg. rectally or orally) immediately following the operation, giving subsequent oral doses of 100 mg. at intervals of three hours for four doses on the first day and six doses on the second day. The drug markedly relieved the postoperative symptoms of eight of twenty-eight patients. Nine patients were considerably relieved, and eleven, moderately so. There were eight relapses occurring after discontinuation of the drug and all of these were successfully relieved by readministration. Only four of the twenty-eight patients suffered a severe nystagmus on the day of the operation and none had frequent vomiting. On the second postoperative day, only one suffered from moderate vertigo. Four had slight nausea, none vomited and only five presented a slight nystagmus. Almost all of the patients were out of bed by the second to fourth postoperative day, with sixteeen able to tolerate a soft diet. The control patients suffered severe vertigo, nausea and nystagmus with frequent vomiting on the first day, with none able to tolerate a liquid diet until forty-eight hours postoperatively.

Dramamine was next used in radiation sickness by Beeler et al,[208] who treated eighty-two patients with doses of 100 mg. thirty to sixty minutes before and three hours after treatment. The total dose was 200 to 400 mg. Initially, all patients experienced nausea and fifty-three vomited. With Dramamine, vomiting ceased in twenty-one in whom there was no nausea or prostration. In forty-four more patients, there was no vomiting but some nausea. Four patients had mild discomfort, while four of thirteen patients, who could not retain and absorb the drug because of vomiting, obtained slight or no relief. Twenty-three patients were used as controls, with results being reported as excellent in none, good in three, fair in nine and poor in eleven. When placebos were substituted in six patients who responded well to Dramamine, all relapsed. The side effects included drowsiness in fifteen, resulting in a voluntary discontinuation of the drug in three; eight reported a bad taste, two, paresthesias, and one, nausea. Dizziness and drowsiness also occurred in the control patients because of the x-ray therapy or the patient's poor nutritional condition.

In a letter to the editor of the J.A.M.A., Kerman[209] reported that he had used Dramamine for nausea and vomiting following electroshock therapy, the dose being 100 mg. one hour before treatment. It was successful in fifteen consecutive cases, with no failures. Kerman also reported on eight cases of migraine treated with Dramamine, every one of whom reported benefit with the use of the drug. The only side effect was sleepiness. In a letter to the editor of the N.E.M.J., Werner[210] reported on his own Ménière's disease, present for thirteen years. With Dramamine there was a dramatic and immediate cessation of all vertigo and a 75 per cent improvement in tinintus, with some increase in hearing of the left ear. In a third letter, Lamar[211] wrote to the J.A.M.A. that he had used Dramamine in six patients, using the 100 mg. dosage, who had previously shown a severe intolerance to aureomycin, to which they responded with intense nausea and vomiting, the symptoms clearing immediately, the patients being able to tolerate 1,000 mg. of aureomycin by mouth every four hours without discomfort. The drowsiness, when present, could be controlled by coffee.

HISTADYL (THENYLENE)

Since Histadyl and Thenylene are trade names for the same compound, they are reviewed together. In 1947, Pierce and Mothersill[212] reported on the preliminary trial in seventy-seven patients given Histadyl. The drug was found to be most effective in treating urticaria due to drugs, serum and food allergies as well as in hay fever and histamine-induced headache. It was ineffective in bronchial asthma. The side effects described include light-headedness, sleepiness and dizziness. Studies done on blood, heart, liver and kidney function show that doses of 100 to 200 mg. daily caused no evidence of chronic toxicity in the five patients subjected to laboratory tests.

In a subsequent report, Feinberg and Bernstein[213] described Histadyl as a "potent antihistaminic substance," since it benefited seventy-nine of 112 patients with hay fever, forty-four of ninety-five with non-seasonal vasomotor rhinitis, seven of twelve with urticaria, seven of nine with dermographism and also one with pruritus of unknown origin and two of three with pruritus ani. Considerable relief of itching is reported as being reported by eight of thirteen patients with atopic dermatitis. In six of nine patients suffering from pre-asthmatic spasmodic cough, the influence was favorable, although the dyspnea of thirty asthmatic patients was not relieved. Such relief as did occur lasted only two to six hours and was not complete. Although 50 mg. doses orally four times daily were well tolerated, approximately 25 per cent of the 253 patients given such doses described the side reactions as consisting chiefly of sedation, which did not equal that usually produced by Benadryl, but equalled or exceeded that produced by Pyribenzamine. Other side effects were vertigo, nervousness, oral dryness, excitation, insomnia, headache, nausea and diarrhea. As with similar drugs, Thenylene was selectively superior for particular individuals. Martins[214] reported on its use in sixty-one patients, excellent results being obtained in thirty-six of forty-four with hay fever and one with asthma; in four with urticaria, one with pruritus, one with dermatitis, and two with dermatitis venenata, as well as in six of eight patients with hay fever and asthma, the hay fever being relieved, and in one, the asthma. Martins described moderate relief as being obtained in six patients with hay fever and in three with both hay fever and asthma, with the hay fever being improved in one, and in two, the asthma. Of these patients, 57 per cent reported soporific effects, in two-thirds of whom the somnolence was relieved with Desoxyn, to such a degree that a dose of 2.5 mg. was given with each 50 mg. of Thenylene. Among the other toxic reactions described are headache, glossitis, tremor, nausea, dizziness, and dermatitis, all of which subsided when the drug was withdrawn. Similar results were obtained by Friedlaender and Friedlaender,[215] who found that symptomatic relief was afforded for several hours following each dose of the drug in cases of urticaria, hay fever and perennial allergic rhinitis. The results in asthma were not striking. The pruritus of allergic dermatoses in some instances was alleviated. Again, side effects were reported in 25 per cent of the patients, these being chiefly drowsiness, vertigo and gastrointestinal upsets, which were rarely sufficiently severe to warrant discontinuation of the medication. Saletta[216] reported excellent results with Histadyl (50 mg. three to five times daily) for hay fever, and 400 to 500 mg. daily for urticaria. The results were excellent in twenty-one cases of pollinosis and good to excellent in four cases of hives, excellent in one case of serum sickness and poor in one case of asthma. The only toxic reaction noted was a dull frontal headache lasting ten to thirty minutes in three patients. In others, the drug temporarily lowered systemic blood pressure ten to fifteen mm.

In another report, Kierland and Potter[217] used Histadyl (100 mg. three to four times daily) in seventy-eight patients with various types of dermatitis. The best response, as usual, was obtained in patients with urticaria. The other conditions treated included atopic eczema, dermatitis venenata, erythema nodosa, sensitization dermatitis due to overtreatment and mycosis fungoides. Other patients were given Benadryl or Pyribenzamine, or both. All of the drugs were equally effective in urticaria. Ten of the patients preferred Thenylene, although in twenty-two, toxic reactions necessitated withdrawal of the drug. The side reactions described include the usual drowsiness, dizziness, vomiting, headache, insomnia and nervousness, although patients intolerated to one drug could tolerate another. No cumulative effects were noted.

Epstein and Macaulay[218] described Histadyl cream (2 per cent) in the treatment of pruritic dermatoses, the drug relieving eighteen of twenty-seven cases of lichen simplex chronicus, four of seven cases with mild or moderate dermatitis, six of nine cases of eczema of the hands, one of six cases of infantile eczema, one

of two cases of nummular eczema and four of six cases of an unclassified subacute dermatitis. The itching was concurrently relieved in those patients in whom the dermatosis was unaffected. The ointment base alone was ineffective, and there were no side effects, excepting in two cases of atopic dermatitis in whom the ointment seemed to aggravate an acute flare-up. Bereston[219] found that of 104 cases of pruritic dermatoses, 40 per cent obtained relief by application of the Histadyl cream and carbowax for as long as the ointment was applied. His series included disseminated neurodermatitis, in which ten of twenty-eight patients were helped, and twenty-four cases of anal, vulval or scrotal pruritus, of whom fourteen were helped. The drug was effective in only two of nineteen patients with contact dermatitis, four of twelve patients with localized neurodermatitis, and eleven of twenty-one with eczematoid dermatitis. Fourteen patients in all, of the various groups described, improved and with the carbowax base alone. In no patient was there any toxic reaction or contact dermatitis.

The toxic reactions are delineated by Snyderman[220] whose patient, a twenty months' old male child, accidentally ingested 800 mg. of Thenylene. Cyanosis, unconsciousness and convulsions appeared, to be followed by a period of cardiorespiratory depression. Normal supportive measures and a short-acting barbiturate caused improvement in twelve hours and complete recovery in twenty-four.

In view of the fact that patients taking Thenylene complained sufficiently often of nausea and epigastric distress, the use of enteric-coated tablets was employed. Hartman[221] administered such tablets to 107 of 112 patients who had obtained relief from the uncoated tablets, the coated tablets being effective in preventing the allergic symptoms for ninety-five patients in this group. The gastrointestinal side reactions were abolished in seventeen of the nineteen patients, who had previously responded to the uncoated tablets with nausea and vomiting. The other usual side reactions were present in sixteen of these patients. Of 206 subjects treated with the uncoated tablets, 112 had moderate to complete relief or prevention of symptoms. An increased effect of Histadyl was described by Mothersill,[222] who gave one group of patients Histadyl alone and another, Histadyl (25 mg.), with ephedrine (8 mg.). Of the patients taking the combination, 33 per cent reported complete, or almost complete, relief. Of the patients taking Histadyl alone, 15 per cent reported drowsiness, whereas of those who took the combination, only 9 per cent reported mild drowsiness.

A new use for Histadyl was described by Selecman and Miller,[223] who described a patient with thrombophlebitis migrans of twenty-five years' duration. The patient had not responded to previous therapy, bedrest, heparin, sulfonamides and vein ligation. He was entirely relieved of any signs or symptoms of venous inflammation by 50 mg. three times daily with 100 mg. at bedtime for seven days.

HISTAPHENE

Histaphene is represented in the literature by a single preliminary note by Lambelin,[224] who used the drug in fourteen patients varying from twenty-three to seventy-four years of age, who suffered from eczema, contact dermatitis, lichen planus, relapsing urticaria, prurigo, pruritus, or dyshydrosis of the hands. The results paralleled those usually obtained with the other antihistaminic agents. There was a rapid progression of the lesions in acute cases, and a lasting improvement in chronic cases. Only one patient reported drowsiness.

HYDRYLLIN

The poor effects achieved with antihistaminic agents in bronchial asthma led to the combination of Benadryl (25 mg.), and aminophylline (100 mg.) in the single compound termed Hydryllin. Segal et al[225] found that there was approximately 80 per cent protection against histamine-induced bronchospasm in five patients, two hours after oral administration of two tablets. The protection lasted approximately

five hours. In mecholyl-induced spasm there was a 40 per cent protection in six patients given such treatment, the maximum protection occurring in three hours. Brown and Brown[226] administered Hydryllin as one or two tablets three or four times daily to 121 patients, noting improvement in ninety-seven. The highest degree of relief occurred in 82 per cent of the pollen and infectious asthma patients. Drowsiness or dizziness was present in 26 per cent of the patients. Other side effects include gastrointestinal disturbances, salivary duct spasm, shakiness and wheezing. In 21 per cent of the patients, the drug was discontinued because of these toxic effects. Levin and Moss[227] treated twenty-two patients with bronchial asthma of the type not complicated by bronchial infection with two to nine tablets daily, reporting that four obtained 100 per cent relief and twelve, 50 to 75 per cent relief. The freedom from symptoms lasted 3-6 hours following each dose. In three additional patients with asthma complicated by infection, only one was relieved, and in twenty-three patients with seasonal hay fever, only two reported 100 per cent relief and eighteen, 50 to 75 per cent relief. In sixteen patients from all three groups there were side reactions of sleepiness, dizziness or nausea.

A comparison of Hydryllin and Trimeton was made by Manace,[228] who reported 60 to 65 per cent relief of asthma in thirty-five patients with 75 per cent relief of sixteen with hay fever, and 75 per cent of twelve vasomotor rhinitis. The chief side effect was drowsiness. In patients aged six to sixty-two years, Trimeton gave 60 per cent relief to twenty-four patients with asthma, to 75 per cent of twenty with vasomotor rhinitis, and to 80 per cent of forty-six with hay fever, as well as to 70 per cent of ten with urticaria. Drowsiness was also experienced in about half the patients affected by Hydryllin.

The effect of Hydryllin on the skin was investigated by Perry et al,[229] who believed that histamine iontophoresis was superior to histamine intradermal injections, scratch tests or skin temperature changes for testing histamine antagonism. Of six groups of ten subjects each, one group received placebos. Each of the other groups received Hydryllin and other antihistaminic compounds, which by this test could be ranged in the following decreasing order of activity, namely, Hydryllin, Pyribenzamine, Benadryl, ephedrine sulfate and aminophylline. Pillsbury et al[230] administered two to twelve tablets of Hydryllin to 154 patients suffering from a number of skin conditions. They report the combination of Benadryl and aminophylline as being efficacious in acute and chronic urticaria, angioneurotic edema, penicillin dermatitis, dermatitis medicamentosa, with some patients with contact dermatitis and atopic eczema achieving relief. Patients with eczematous dermatitis, pruritus vulvae and ani, localized neurodermatitis, lichen planus, erythema multiforme, psoriasis, and neurotic excoriations, were not relieved. In all, approximately 20 per cent of the patients reported side reactions. Five patients apparently obtained as much relief from the placebos as from Hydryllin. The authors state, and wisely so, that much larger series of patients must be accurately evaluated before any final conclusion is reached as to the effect of the drug on exfoliative dermatitis and dermatitis herpetiformis.

Of more than passing interest is the report by Falk and Newcomer,[231] who describe a typical case of Loeffler's syndrome, the patient being treated by penicillin in oil and wax. There were chills, fever and a cutaneous reaction with severe leg pains and giant hives at the injection site by the end of the third week. Coincident administration of Hydryllin every four hours lowered the temperature to normal, but did not relieve the leg pains. A second patient, presenting a Loeffler syndrome was treated symptomatically with Pyribenzamine which was found to be as effective.

LINADRYL

The results with Linadryl are similar to that of Benadryl, the drug being probably about one-half as effective, weight for weight. McGavack et al[232] administered the

drug in doses up to 75 mg. daily, with 12.5 per cent of 143 patients with allergic diseases reporting complete symptomatic relief, and 48 per cent, partial relief. In one-third of the patients, the skin histamine response decreased after one week of therapy with 600 mg. daily. Depressant effects occurred when 800 mg. was given daily for one week. In 17.2 per cent of the patients side reactions were described as drowsiness, dizziness and blurred vision, headache, confusion, fatigue and weakness, diarrhea, heartburn, dry mouth, abdominal cramps, palpitations and jumpiness.

NEO-ANTERGAN

Although the animal experimentation with Neo-Antergan is unusually detailed and complete, only selected clinical papers will be reviewed. Early in 1948, Hunter and Dunlop[233] reported on the use of Neo-Antergan (0.1 to 0.3 gm. for children and 0.3 to 0.6 gm. for adults) administered to thirty-five patients with frequent attacks of "allergic asthma." The drug was given to alternate patients, placebos containing starch and lactose being used to treat those not receiving the drug, the procedure being reversed after three months. Eleven patients apparently improved with both Neo-Antergan and the placebos, and of these, three received further treatment with the drug, but improvement was not maintained. In four patients, the asthmatic state was definitely worse during Neo-Antergan therapy, and three patients could not be followed-up adequately. The side effects described include nausea, drowsiness and dizziness. Two months later, Herxheimer[234] reported that the vital capacity had been increased in twenty-one of thirty-nine patients with bronchial asthma following Aleudrine (Isuprel) therapy, the patients receiving 0.02 to 0.06 gm. of the drug perlingually, or 1, 3, or 5 per cent solutions by inhalation. Anthisan was reported in the same study as being successful in twenty-six of thirty patients with bronchial asthma, in that it permitted them to sleep without any wheezing all night. The doses given range from 0.07 to 0.7 gm. of the drug orally, or 10 per cent of the solution used by inhalation. Tolerance did not develop in patients given the drug only once daily. Side reactions described include drowsiness, nausea and diarrhea. In a later communication, Herxheimer[235] defended this conclusion that Neo-Antergan increased the vital capacity of asthmatic patients against Dunlop and Hunter, who had stated that the increase was insignificant and that tolerance to the drug did not develop. He stated that his experience indicated that increases in vital capacity, although small, were significant and that tolerance did develop, suggesting that Dunlop and Hunter had used suboptimal doses of the drug. In a third communication, Hunter[236] reported on the inhalation of histamine, mecholyl or allergenic extracts, and the attacks thereby produced recorded by a spirometer. He stated that in a number of normal and asthmatic subjects, the bronchial obstruction and the bronchospasm could be effectively prevented by prophylactic Neo-Antergan or Phenergan. No protection was achieved, however, for severe attacks. He feels that the individual effective antihistaminic substance and its dosage must be found in each case by trial and error and when so found night doses can be combined with day doses of ephedrine, while any additional acute attacks can be checked by Isuprel. The combination is stated to have been used successfully in a number of patients who had been rendered capable of regular employment.

Neo-Antergan was carefully studied by Southwell[237] in twenty-five asthmatic patients and in fifteen with hay fever, the patients being of the extrinsic type with minimal infection and lung damage. Each was graded at the outset according to the severity of past symptoms, with the first grade including patients whose attack rate was less than one monthly, while the sixth grade patients were unable to work, owing to continuous wheezing. The trial lasted eight weeks, the patients being examined at the end of each week. For the first two weeks, placebo tablets were given and thereafter, true and placebo tablets were alternated at intervals of two to three weeks. The dose for Neo-Antergan for the first three days was 0.1 gm. three times

daily, increasing subsequently to 0.3 gm. three times daily. At the end of a trial period, the average grading figures were calculated for the weeks on placebo and medicated tablets, and these were regarded as symbolic of the weekly severity of the patient's asthma. The average weekly grade numbers for the series of patients were three to six when treated and 3 to 6 when untreated on either placebo or medicated tablets, respectively, proving Neo-Antergan of little or no value in the treatment of bronchial asthma. The figures illustrate the importance of adequate control with placebo tablets. The author states that no beneficial effect was noted in the milder cases or in those of recent onset, and the sedative effect did not benefit the asthmatic attack rate. Two patients were greatly improved by the placebo tablets. In a similar trial in hay-fever patients sensitive to grass or tree pollens, the average weekly gradings were 3.8, 3.73, and 1.5 when untreated and on dummy and real tablets, respectively. The patients who responded regarded the effects as "equal to any but the most successful desensitization course." Neo-Antergan was therefore considered of real value in the symptomatic treatment of hay fever. Twenty-three of the forty-two patients reported side effects, nausea in ten, nausea and drowsiness in six and drowsiness in four, to list some of the untoward reactions.

According to Calder,[238] of thirty-eight patients with vasomotor rhinitis, twenty-nine reported moderate to good relief of symptoms, as did six patients with hay fever taking Neo-Antergan in doses of 0.1 gm. three times daily for five days and, in the absence of untoward reactions, 0.2 gm. tablets three times daily for ten days. Reduction in dosage caused partial return of symptoms, and in this group, the incidence of untoward reactions, especially drowsiness, was very low. On the basis of treating 147 patients with hay fever, Weiss and Howard[239] recommended preseasonal or perennial hyposensitization as supplemented by 50 to 100 mg. tablets of Neo-Antergan or Pyribenzamine, three or four times daily, as required. Neo-Antergan is noted as producing a greater number of side reactions and of being slightly less active than Pyribenzamine. In perennial vasomotor rhinorrhea, Reid and Hunter[240] reported nineteen of thirty-five patients achieving complete relief without relapses during a six months' follow-up period, with twelve achieving some relief, and four, no relief, the dose being 0.6 gm. daily for four weeks. In some cases, 0.2 gm. daily was sufficient. Four patients required 0.8 gm. daily for complete relief. On placebo therapy, 5 per cent of the patients obtained complete relief, 35 per cent some relief and 60 per cent no relief, a total of 40 per cent being improved by placebo medication.

In this country, work by Schwartz et al[241] on 141 allergic patients suffering from hay fever and vasomotor rhinitis, as well as bronchial asthma, showed that over-all symptomatic relief could be obtained in eighty-seven patients, fifty-four reporting no relief. The poorest results occurred in bronchial asthma. Thirty-five patients suffered from toxic reactions, including drowsiness, nausea, diarrhea, abdominal cramps and headache, in some cases so severe that it was necessary to discontinue the drug. The patients were maintained on a 50 mg. three times daily dose, at which level 24.8 per cent showed side reactions. The best results occurred in sixty-seven of ninety-six cases of hay fever. This dropped to 59.1 per cent (thirteen of twenty-two cases) in patients with vasomotor rhinitis. Only two or fifteen patients with bronchial asthma responded.

Reid and Hunter[242] followed up nineteen of thirty-five patients who had been successfully treated for perennial vasomotor rhinitis with Neo-Antergan six months previously. All were still symptom-free. Of seventeen patients who had taken medication fifteen months previously, fourteen were still symptom-free, and three presented a return of symptoms. Of the seventeen, thirteen were studied as regards nasal mucosa, the type of secretion and whether eosinophilia was present in biopsy material. Two stated that they had been occasionally upset during the fifteen months' period, while the others seemed entirely well. In seven, the nasal mucosa appeared to

be normal, while in six it was pale and moist. The nasal secretion of eleven was dry, while three had mucoid secretion. Biopsy tests were negative in eight, positive in one and borderline in four. The positive case showed a considerable eosinophilia in the biopsy material and was considered to be an allergic individual.

A larger series studied (211 cases) was reported upon by Tobias and Grindon,[243] who administered Neo-Antergan in 25 to 50 mg. doses three times daily. Some patients with atopic eczema received doses of 400 mg. daily, while in acute urticaria the usual dose was 50 mg. four hourly with 100 mg. at bedtime. In acute urticaria, seven of sixteen patients were "cured," with seven improved temporarily and two showing no benefit. In chronic urticaria, four of five reported "cure" and one, no benefit. In passive urticaria the pruritus of four patients was relieved, but not of the other two, the eruptions being unaffected. In ten children with atopic eczema, five showed marked improvement, four moderate, while five patients with generalized eruptions found their pruritus relieved by Neo-Antergan. Delayed reactions occurred in adults with atopic eczema, who were not benefited, the pruritus not being diminished until the drug had been taken for at least thirty days. In two patients with an exfoliative dermatitis neither the eruption nor the pruritus was affected, nor were eleven patients with pruritus ani relieved. There were no effects in thirty-six patients with disseminated neurodermatitis, in four with nummular eczema, in four with erythema multiforme, or in two with dermatitis herpetiformis. Moderately toxic symptoms were reported in ten patients and mild side reactions in thirty-two. The side effects included nausea, dizziness, paresthesias, nervousness, insomnia, weakness, headache, cramps and heartburn. The failure of relief with oral medication may be corrected by topical application as shown in the report by Rasmussen,[244] who treated twenty patients with pruritus ani, with Neo-Antergan cream, 2 per cent. Twelve of the patients obtained excellent results, three good results, five not being benefited. The cream was applied nightly or whenever itching was present, relief occurring within two to three minutes and lasting ten to twelve hours. In addition, the ointment relieved the symptoms of seventeen other patients suffering from pruritic dermatoses, provided the lesions were slight and situated in "delicate skin areas." It was poorly tolerated in exudative eczema. That the drug was readily absorbed was proven by the fact that for one hour afterwards its presence in the skin reduced histamine whealing induced by electrophoresis. The author, however, attributes the anti-pruritic properties to the anesthetic effect.

The miscellaneous effects of Neo-Antergan include its use in the pruritus of jaundice, as reported by Hunter and Dunlop.[245] The dose is 0.2 gm. every four to six hours. Four patients with iodine reactions seen following bronchography or preoperative disinfection of the skin by Boucher and Lafuma[246] were similarly relieved. The drug has also been used in the management of liver and insulin sensitivity by Hunter and Hill.[247] Five of nine cases required 300 mg. one hour before the injection, following which two patients had no reactions, two a modified reaction and one a severe reaction. In four additional patients, two of whom reacted severely, 1 gm. of Anthisan given twenty-four hours before the liver injection resulted in one patient showing a mild reaction and three being free of symptoms. One patient, severely sensitive to insulin, was relieved after four days of treatment, the dose varying from 500 to 800 mg. daily. An additional two mild reactors, with local lesions were cured, after a ten-day course. The authors suggest wisely that the drugs should be given for longer periods of time to enable spontaneous desensitization to insulin to take place.

Brown et al[248] used Neo-Antergan in radiation sickness. Their negative report showed that doses of 0.6 gm. daily did not prevent the appearance of the condition in sixteen of seventeen patients, treatment being instituted five days before postoperative roentgen irradiation for breast carcinoma. The administration had to be discontinued in many patients because of severe constitutional reactions. In five

patients, an erythema developed which disappeared upon withdrawal of the drug. On the other hand, in motion sickness, fifty-one of 134 seasick individuals given Neo-Antergan, 100 mg., and Hyoscine 1/100 gr., alternately, preferred the Neo-Antergan, while forty-two individuals preferred the Hyoscine. McEvedy,[249] on the basis of these studies, recommends Neo-Antergan, one tablet three times daily. In this regard, the notes of Tyler (*op. cit.*) regarding Dramamine should be noted. The comparison of Hyoscine, Dramamine, and Phenergan with Neo-Antergan was done by Beaumont.[250] Of his 100 patients, 20 per cent had failed to respond to Hyoscine and 7 per cent to Dramamine, Neo-Antergan by suppository and orally relieved these patients whose average duration of vomiting prior to medication was thirty-six hours. Following the Neo-Antergan, Phenergan was given in doses of 25 mg. No untoward reactions, excepting drowsiness, occurred. The author makes no mention of the fact that seasickness is a self-limiting condition, the patients and the control individuals all acquiring their "sea legs" within a comparatively short period of time.

Dougray[251] treated ninety-four pregnant patients who complained of nausea and/or vomiting, with Neo-Antergan, two to seven tablets daily, or 0.025 gm. Phenergan, three times daily. Twelve were unchanged, four were improved and seventy-eight reported cure. One thirty-four-year-old patient who had suffered from intense continual vomiting during the tenth week of pregnancy, no response having been noted to phenobarbital, vitamin B-1, intravenous glucose saline, or glucose by mouth, responded to Phenergan and Neo-Antergan given on the first, third and tenth days of hospitalization, the dose of Phenergan being one tablet morning and night initially, increased gradually to seven tablets daily. Anthisan was used in doses of 0.1 gm. three times daily. Drowsiness appeared at the top dose of Phenergan, requiring amphetamine sulfate (5 mg.) each morning, the drowsiness being the chief side effect of both drugs in almost all patients.

On the basis that acute nephritis might be an allergic response to bacterial toxins, Craig et al[252] administered Neo-Antergan (0.1 gm. three times daily) to eight children, aged two to nine years. By the eighth day, two children, in whom the condition had been mild, the symptoms being hematuria, albuminuria and puffiness around the eyes, were noted as cured, while six more patients with more marked urinary pathology, including increased blood urea, azotemia, marked edema, hypertension, and hypertensive convulsions, were cured in about fifteen days. One patient relapsed, requiring the readministration of 0.1 gm. every four hours to produce a complete cure in ten days. Three control individuals with a milder form of nephritis and six with moderate or severe symptoms not treated with Neo-Antergan were cured on an average of twenty-one and 128 days, respectively. All of the patients in either group who showed signs of active infections received penicillin or sulfonamides, although the nephrotic symptoms were not altered by the administration of these drugs. In a later report, Clark[253] described eight patients with nephritis, including two with hypertensive convulsions treated for five to forty-five days with Neo-Antergan (0.3 to 0.5 gm. daily.) Full recovery was seen in six to twenty-one days, the average being thirteen days, while that for six control patients was ninety-two days.

To add to the confusion regarding "cold cures," Paton et al[254] gave twelve subjects, who had developed colds in the preceding twenty-four hours, Neo-Antergan (100 mg. three times daily) for two days. Four reported improvement, one was unchanged and one was undecided. The average duration of the cold was 6.5 days. Ten additional patients were given placebos. Of these, four claimed to be improved, four unchanged and two undecided. For the second group the average duration of colds was 6.2 days. The clinical conditions of both patients were so similar that the examiner could not decide which patient had been given the drug and which the placebo.

Among other miscellaneous conditions treated with Neo-Antergan, are two cases of Stevens-Johnson syndrome by Salomon,[255] the milder case showing complete re-

covery after three days of 50 mg. doses four times daily, while the more severely ill patients responded slowly. Three other cases of the same type, one with acute otitis media, is also said to have responded. Herpes zoster is reported as responding to Neo-Antergan by Hornigsberger.[256]

Two fatalities due to Neo-Antergan have recently been reported, the first by Tobias,[257] whose patient, a twenty-one months' old child, swallowed 600 mg. The second is by Jaulmes[258]and is reported only by title in the Swiss literature, the original paper not having been examined. A third case is known to the present author, the data to be published in the near future.

NEOHETRAMINE (NH 188)

In an ingenious experiment using fluorescin and histamine intradermally, Bukantz and Dammin[259] were able to demonstrate that the fluorescence under ultraviolet light lasted for thirty to forty-five minutes in normal individuals. An injection of fluorescein and histamine (1:10,000) caused fluorescence in four to ten minutes. A mixture of the two with Benadryl (1:2000) fluoresced for only twenty-five to thirty-five minutes, demonstrating the neutralizing effect of the Benadryl on the histamine. When Neohetramine (188) was used in the same way, it was found to be approximately equal to Benadryl in activity. Skin sites in both man and dog were used, concentration of 1:5000 of the antihistaminic drugs inhibiting the fluorescence due to intravenous administration of 3 ml. fluorescein (5 per cent.)

By intraperitoneal toxicity tests in mice, Neohetramine was found to be about half as toxic as other antihistaminic drugs by Scudi et al,[260] the usual bronchiolar, capillary, dilator, smooth muscle and vasopressor effects of histamine being markedly inhibited. The other experiments are only mentioned because it was discovered that in low concentrations the drug had no effect on smooth muscle, while in high concentrations it induced contractions. It caused a transient irritant action of the eye, accompanied by local anesthesia. It did not alter the action of epinephrine, but decreased the salivary secretion, caused ventricular depression, bradycardia and transient vasodepression. Further experimental studies with guinea pigs by Friedlaender and Friedlaender[261] showed that 3.0 mg./kg. Neohetramine protected 70 per cent of ten guinea pigs from anaphylactic shock when given fifteen to twenty minutes prior to the shocking dose of horse serum. In a continuation of the work, these authors showed that among 140 patients, the drug was beneficial to eleven of forty with bronchial asthma, twenty-six of fifty with vasomotor rhinitis, thirty-seven of forty-eight with hay fever, six of six with acute urticaria, two of four with chronic urticaria, none of three with atopic dermatitis, one of two with contact dermatitis, and three of four with unclassified dermatitis. Three patients with allergic headache and one with allergic conjunctivitis were not helped. The optimum dose in children six to twelve years of age was 50 mg., and for adults, 100 mg. every four to six hours. Although the drug was discovered to be useful in patients unable to tolerate other antihistaminic agents, nevertheless, untoward reactions were observed in seventeen patients, five complaining of drowsiness, five of gastrointestinal irritation, three of dizziness, and one each of weakness, pruritus, diplopia and tinnitus. In human subjects, Bernstein and Feinberg[262] showed that the application of the solution locally inhibited the wheal and flare from applied histamine, 27 per cent as compared to Pyribenzamine. In a group of 148 patients suffering from 184 allergic complaints, doses of 50 mg. given continuously two to four times daily when symptoms were continuous, and administered in single doses for isolated attacks, brought relief to thirty-one of sixty-five patients with seasonal hay fever, with twenty-one of thirty requiring 100 mg. Fifteen of thirty-four patients with perennial rhinitis were relieved by 50 mg., with eight of fourteen needing 100 mg. The drug did not consistently lessen the frequency or severity of individual attacks of bronchial asthma. The incidence of side effects is noted as being less than with most other antihistaminic agents, occurring

in only 9 per cent of 100 patients on the 50 mg. dose, and 15 per cent of forty-eight patients taking 100 mg. No blood pressure, blood or urine changes were noted in eight patients who took the drug three times daily for four to six months. Similar clinical results were reported by Waldbott and Borden,[263] who used the drug in 279 patients, reporting good results in ninety-one, and some improvement in eighty-two. The patients presented conditions as varied as allergic conjunctivitis, allergic rhinitis and hay fever, migraine, urticaria, atopic dermatitis, contact dermatitis and bronchial asthma. The best results were obtained in allergic nasal disease and urticaria, twenty-nine patients complaining of dizziness and drowsiness about one hour after a 50 mg. dose. Several patients presented muscular twitching in twenty minutes.

Aaron and Criep[264] not only experimented with guinea pigs, but also did toxicity studies on seventeen patients, who were given Neohetramine (300 mg. daily), while thirty-seven patients were given the same dose of Thephorin, each for four days. One patient, seventy years of age, with heart failure, showed an inversion of T waves in lead C-V4, which reverted to normal upon withdrawal of the drug and on readministration again became inverted. Another patient, who took Thephorin, showed an inverted T wave during its administration, the wave becoming upright after the medication had been discontinued. No other patients showed any electrocardiographic changes. Whealing responses with ragweed and histamine were inhibited by Neohetramine, Thephorin, or Pyribenzamine, (200 mg.) given one hour orally before the test. Side reactions occurred in 23 per cent of the patients taking Thephorin and 10 per cent of those taking Neohetramine, nervousness and nausea predominating. There was some insomnia. The results are recorded as good in allergic rhinitis, either perennial or seasonal, and in urticaria and angioneurotic edema. The drug was of some value in the management of asthma, atopic and contact dermatitis. In a later communication, Criep and Aaron[265] reported on 243 children and adults suffering from hay fever, allergic rhinitis and urticaria. Two hundred and thirty-two infants were given Neohetramine elixir (25 to 50 mg.) every four hours. Of these, twenty-eight of sixty-one with allergic rhinitis, twenty-five of forty-seven with hay fever, twelve of twenty-two with urticaria and angioneurotic edema, and six of sixty-six with bronchial asthma were relieved, as were three of twenty-one with atopic eczema, one of nine with contact dermatitis, three of three with physical allergy. Three patients with gastrointestinal allergy were not affected. Side reactions occurred in eighteen patients and consisted of the usual restlessness, insomnia, constipation, rhinorrhea, drowsiness and headache.

In a report by Schwartz and Reicher,[266] the dose was 50 mg. one to four times daily with occasional patients taking 100 mg. three to four times daily. Relief of symptoms was seen in thirty-eight of fifty-three patients with hay fever, fourteen of twenty-two with vasomotor rhinitis, ten to twenty-four with bronchial asthma, three of five with chronic urticaria, one of six with atopic eczema and one case of pruritus (unspecified.) Mild reactions were noted as occurring in 17.2 per cent of these patients. In a later report, Schwartz[267] compared the side effects of Neohetramine with those seen following Antistine, Benadryl, Histadyl, Neo-Antergan and Pyribenzamine, the successive number of cases being 97, 217, 89, 141 and 126, with eleven patients receiving Neohetramine. Although these numbers are not significant and not comparable, the percentage of side reactions are given, respectively, as 22.7 per cent, 61.3 per cent, 20 per cent, 24.8 per cent, and 35.7 per cent. Those for Neohetramine were 7.2 per cent (as stated above, of eleven patients.) In a third report by Criep and Aaron,[268] 72 per cent of 124 patients with hay fever, 80 per cent of forty-one with allergic rhinitis, 63 per cent of thirty-three with bronchial asthma, 82 per cent of eleven with atopic dermatitis, 75 per cent of twenty with urticaria, and 83 per cent of six with migraine had moderate to complete relief from Neohetramine (50 mg. every four hours.) All of the patients with contact dermatitis were helped. Ten per cent of the patients complained of side reactions, including dizziness, diar-

rhea, constipation, headache, nervousness, nausea and insomnia. The side reactions were fewer than those caused by Pyribenzamine or Benadryl. The Neohetramine was considered slightly more active than Benadryl, but not as active as Antergan. The vital capacity improved 25 per cent or more in seven of twenty-one patients with various types of bronchial asthma following doses of 50 mg. Eight improved clinically and seven of these presented increased vital capacity, which totalled 79 per cent in one patient.

Neohetramine, of course, received its greatest publicity in its use for the treatment of the common cold. Tebrock and Mitchell[269] treated 1,000 subjects prophylactically with Neohetramine (Anahist), 25 mg. being given four times daily throughout the season. They stated that the tablet prevented the occurrence of the common cold in a large percentage of persons who ordinarily would have suffered one or more colds. In patients who took the drug promptly within the first twenty-four to forty-eight hours, the drug either aborted the cold or stopped the progression of symptoms to a point where there was no longer acute discomfort, the individuals remaining on the job without exposing others to their ailment. In a study by Arminio and Sweet,[270] 100 subjects were treated for 180 days, with Neohetramine (50 mg.), once, twice or three times daily. The respective numbers free of cold symptoms of each group were eighty-three, ninety and ninety-two. Of those who suffered with colds, five, seven, and six, respectively, had only the first phase, lasting twenty-four hours. None in the first group, none in the second group and one in the third group who took the Neohetramine three times daily suffered the first and second phases of the cold, lasting forty-eight hours, and twelve, three, and one suffered all three phases of colds, lasting three to seven days. In a control group of 300 patients given placebos, fifty-nine were free of cold symptoms; none suffered the first phase alone, sixty-two suffered from the first and second phases, and 179 had all three phases with malaise, cough and purulent discharge. Of the cold group, eleven developed complications such as pneumonia, bronchitis, and sinusitis. The average duration of colds among forty patients treated with Neohetramine three times daily for three days, starting during the first phase of the cold, was 1.2 days. Of forty-six individuals starting during the second phase, the average was 2.8 days; and among eighteen, whose treatment was started during the third phase, the duration was 5.1 days. Reactions were mild, nine of the 100 patients taking the drug three times daily complaining of dryness of the throat and sneezing, and two of mild nausea. All symptoms were alleviated by decreasing the dosage to 50 mg. daily. Needless to say, no such results have been achieved by other physicians treating colds prophylactically or therapeutically, and, again, time alone can give the true picture of the use of these drugs in common colds.

The last report is that of Judd and Henderson,[271] who considered the inflammatory reaction characteristic of tuberculosis as due to allergic causes, and administered Neohetramine for periods up to seven months to thirty patients with tuberculosis. Improvement was noted by x-ray as well as clinically, the coughing and expectoration decreasing with the patient's appetite and weight increasing. On early discontinuation of the drug there was a mild progression of lesions and a general recrudescence.

PERAZIL

The first work on the pharmacological qualities of Perazil on humans by Jaros et al[272] dealt with its long-lasting effects. Thirty subjects, sixteen allergic and fourteen non-allergic, were scratch-tested with histamine solutions 1:4000 to 1:512,000; fifteen received Pyribenzamine (100 mg.) and fifteen, Perazil in the same dose. After a suitable recovery period the tests were repeated, excepting that the patients who received Perazil now received Pyribenzamine and vice versa. In one test with the 1:256,000 dilution of histamine, the wheals returned in fourteen of fifteen patients given Pyribenzamine within four hours, while only two of fifteen patients given

Perazil had similar wheals, the effects of the latter in some patients lasting about thirty-two hours longer. In a cross-over experiment, four of fifteen patients treated with Perazil had wheals 0.5 to 2 mm. in diameter, while thirteen of fifteen given Pyribenzamine had wheals 0.5 to 2.5 mm. in diameter. Sixty-three doses of Perazil were followed on seventeen occasions with drowsiness, while twenty-four of fifty-six doses of Pyribenzamine caused somnolence, the reactions following Perazil being much milder. Blood pressure studies on three of the subjects showed no significant changes on doses of 400 mg. In a second communication, Jaros[273] reported on the complete relief achieved after one dose on twenty-two of twenty-three patients with hay fever, eight of eight with atopic dermatitis, eighteen of twenty-one with vasomotor rhinitis and six of six with acute urticaria. The good effects lasted twenty-four hours. Three of three patients with contact dermatitis, two of thirteen with bronchial asthma, two of two with sinusitis, one of one with chronic urticaria and six of seven with other allergies obtained excellent relief. Moderate improvement was seen in eight patients with bronchial asthma and two with vasomotor rhinitis and one with hay fever, while the remainder were not improved. The greatest relief was seen in patients given the combined hyposensitization and Perazil treatment. Side effects, which were mild, occurred in only four patients, who were drowsy. Two patients, suffering from severe serum sickness reactions due to penicillin and reacting toxically to other antihistaminic agents, were treated with Perazil, the first for seven days and the second, for sixteen hours, with marked relief.

The pharmacological studies on animals by Castillo et al[274] were interesting in that they showed Perazil to be four times more antihistaminic than Benadryl, as tested by the isolated guinea pig tracheal chain, the drug being compared with Benadryl, Tagathen, Neo-Antergan, Thenylene, and Pyribenzamine. For comparative purposes, the intraperitoneal LD_{50} of Perazil in mice was found to be 137 mg./kg., while that for Neo-Antergan was 115, Tagathen 105, Thenylene 77, Pyribenzamine 67 and Benadryl 69 mg./kg., respectively. The chronic toxicity of Perazil in rats and dogs was extremely low. The monochloride compound (AH 289 Abbott) was shown to be equal in effect by Roth et al,[275] 50 mg. doses given orally causing marked reduction in the histamine flare in 9 human subjects for as long as twenty-four hours, while the protection afforded by Thenylene and Pyribenzamine lasted only eight hours.

The clinical evaluation by Brown et al[276] concerned 186 patients treated with doses of 12.5 to 200 mg. daily. Of these, seventy-five had hay fever, seven vasomotor coryza, fifteen urticaria, seven intrinsic bronchial asthma, eight atopic eczema, two vernal conjunctivitis, one dermatitis herpetiformis, two psoriasis, one generalized pruritus, fourteen contact dermatitis, eighteen bronchial asthma and atopic dermatitis, thirty hay fever and bronchial asthma and one hay fever and poison ivy. Others suffered from miscellaneous syndromes, such as a combination of the above. Side reactions were seen in only five of seventy-five patients with hay fever, in one of thirteen with urticaria, in three of thirty suffering from hay fever and bronchial asthma and one of eighteen with bronchial asthma alone, usually being associated with doses in excess of 100 mg. daily. Although the results were not given in percentages they were much better than those achieved by any other antihistaminic agent so far studied by the same group of physicians.

PHENERGAN

In 1946, Halpern and Ducrot[277] published a preliminary note on a new chemical series possessing a powerful antihistaminic and anti-allergic effect, namely, the derivatives of Thiodiphenylamine. These differed from Antergan and Neo-Antergan, which are, respectively, derivatives of aniline and pyridine. The new drug, Phenergan, was said to be less toxic than Neo-Antergan in mice and have a more powerful antihistaminic effect, inasmuch as equivalent doses of Neo-Antergan and Phenergan

protected guinea pigs against only eighty lethal doses of histamine as against 1,500 lethal doses. The drug was described as more specific, inasmuch as there was no antagonism to acetycholine. In six cases of urticaria, resistant to other drugs, the results were excellent, and there were no gastric disturbances or alteration of the blood picture over a period of six weeks. The only side reaction was somnolence. The dose was smaller than that employed with previous drugs, the initial dose being 0.25 gm. given in five equally spaced doses, preferably after meals. The pruritus was described as disappearing in thirty minutes and the eruption within an hour. In two cases of angioneurotic edema and one case of eczema, similar satisfactory results were observed. In a later communication, Halpern et al[278] showed that, in animals, Phenergan was two to three times as effective as regards duration of protection, as were either Antergan or Neo-Antergan. Like other antihistaminic agents, however, Phenergan failed to modify the action of histamine on gastric, pancreatic or salivary secretions and although the animals were protected against 1,500 lethal doses of histamine, nevertheless some developed gastric ulcers, which in some cases, fatally perforated the peritoneum within twenty-four hours. In 1947, Halpern[279] reported that the antihistaminic action of Phenergan was forty times that of Antergan, and its anti-anaphylactic action five times as great. Its effect lasted for about nine hours as compared to larger doses of Antergan and Neo-Antergan which lasted for not more than three to four hours.

In the clinical results by Vallery-Radot et al,[280] all but one case of urticaria responded, as did three cases of urticaria due to serum sickness. Disappearance of symptoms was observed in six to eight cases with angioneurotic edema, and in thirty-six of thirty-eight cases of hay fever. In twenty-one cases of asthma, however, there was no improvement in ten and appreciable relief in seven, with complete disappearance of all symptoms in four. There was no effect in three cases of spasmodic cough, or in five cases of acute eczema. Petechiae, occurring for several weeks, ceased to appear when Phenergan was administered. Four of ten cases of migraine were favorably improved. The cases in which Phenergan failed did not respond to other forms of antihistaminic treatment. There were doubtful or no effects in cases of chronic or subacute rheumatism, infectious arthritis, and tuberculosis. The side reactions, namely somnolence, sometimes accompanied by unsteadiness, vertigo and clouding of the consciousness, are said to disappear after the first few days if treatment is continued with the same dosage, benzedrine being given simultaneously to prevent the reaction. The authors felt that the properties of Phenergan were not entirely explicable on the basis of its antihistamine qualities. Although Gate and Pellerat[281] were able to confirm the efficacy of Phenergan, stating its activity and duration were superior to those of the former products available, they observed that other drugs were preferable because of superior tolerability.

Hunter[282] discussing the clinical use of antihistaminic substances stated that the incidence of toxic effects was much greater with Phenergan than with Neo-Antergan, although Benadryl might be more effective for the relief of itching. He found, however, that ideal treatment consisted of desensitization in addition to the use of antihistaminic drugs, the combined treatment producing 95 per cent relief in the cases studied. Of particular interest is the fact that placebo tablets gave some relief for 34 per cent of a group of patients suffering from perennial rhinitis, Neo-Antergan producing complete relief in 50 per cent. Halpern and Hamburger[283] presented some of the same data in another communication, doses of 20 mg. daily resulting in the disappearance of pruritus and urticaria within thirty minutes to three hours in seven cases of serum sickness, and of joint pains in two of four patients. There was immediate improvement in 108 of 123 cases of urticaria, in all of whom Neo-Antergan had failed to relieve the symptoms. There was improvement in sixteen of ninety cases of true angioneurotic edema, and complete relief in nine allergic of seventy-two patients with asthma, with some improvement in twenty-one non-allergic patients and

no results in forty-two others. There was "vast improvement" in twelve of eighteen cases of prurigo and complete relief in ninety-eight of 124 cases of hay fever, with partial relief in thirty-one. None of seventeen patients with chronic eczema were completely cured, but three of twenty-two cases of acute and contact dermatitis improved rapidly to a complete cure, while others slowly improved. None of three arsenical and one gold erythrodermia patient, as well as others with spasmodic cough, or chronic or subacute rheumatism, were helped. In two patients there was a slight neutropenia and 25 per cent of the patients experienced slight drowsiness, vertigo and instability when standing, including a sensation of drunkenness and decrease in intellectual powers. In a brief report, Vallery-Radot[284] reported that in 180 of 200 patients, symptoms of hay fever disappeared almost immediately following the administration of 25 to 50 mg. of Phenergan. Results were less favorable in sixteen patients. There were no effects in four.

Moindrot[285] described the effects of Phenergan on fifty-seven patients, nine of whom suffered from acute and six of chronic urticaria, four of angioneurotic edema, eight of acute and seven of chronic eczema, with seven additional patients presenting superimposed bacterial infections, eight of generalized and five of local pruritus, and three of herpes zoster. The report states that it has a favorable influence and occasionally cures eczematiform dermatitis of external origin, the itching being diminished or suppressed. The pain of herpes is diminished and the cutaneous evolution is modified. The author considers Phenergan most promising for the treatment of herpes. The drug is stated to cause less gastric irritation than Antergan and its derivatives, and side effects are reported as rare. The oleated Phenergan gave good results when applied locally in three cases of urticaria following serum treatment. It was ineffective or irritating in three cases of eczematous pruritus and three of vulvar pruritus.

For those physicians who may be puzzled by the fact that the number of communications by Halpern is great, it should be pointed out that the same material was evidently presented to a number of journals, all of whom accepted it, including the *Journal of Allergy*,[279] the *Bulletin of the New York Academy of Medicine*,[286] and the *Journal of the Canadian Medical Association*.[283] Other references are therefore omitted for reasons of space, since the clinical material is almost identical.

Phenergan and Anthisan were compared by Bain et al.[287] They discovered Phenergan to be about seven times as active as measured by the reduction of the wheal area for intradermal injections of 10, 1, and 0.1 mg. of histamine given before and at intervals after the injection of the drug. The average times for maximum action of the drug were 120 minutes for 150 mg. of Anthisan and 190 minutes for 25 mg. of Phenergan, while 50 per cent of the activity was still present 430 and 1,360 minutes, respectively. Twenty patients with chronic urticaria treated with Anthisan (300 to 1,200 mg. daily) for one to twenty-four weeks were given Phenergan (25 to 100 mg. daily) for one to thirteen weeks. Anthisan was necessary in three or four-times daily doses, while Phenergan was effective in all patients in a single nightly dose. Phenergan produced mild morning sleepiness in five patients, while Anthisan produced persistent sleepiness, light-headedness, and gastrointestinal disturbances in four patients; fourteen of the twenty patients preferred Phenergan to Anthisan, five had no preference and one preferred Anthisan. On a daily dosage basis, Phenergan was found to be fourteen times more active.

In this country Shulman[288] chose patients who had previously been unsuccessfully treated with other antihistaminic agents and gave a single dose of Phenergan (6.5 to 25 mg. daily) after the last meal. Nine of twenty subjects with perennial vasomotor rhinitis, seven of ten with perennial and seasonal asthma, eight of eight with urticaria, two of four with eczema, three of nine with contact dermatitis and two of four with migraine had good or marked improvement. Seventeen patients complained of dizziness and one of such severe drowsiness that the drug had to be dis-

continued. Herxheimer[289] discovered that in patients with bronchial asthma, the optimum doses for Anthisan were 300 to 500 mg. daily, while with Phenergan and Benadryl, the necessary doses were 50 to 75 mg. Although Phenergan caused drowsiness in some cases, some patients also complained of insomnia. An intravenous injection of 25 mg. was beneficial in thirteen patients with genuine asthma and in four in whom bronchospasm was induced by inhalation or mixed inhalants or mixed pollens. In two normal subjects, in whom the vital capacity was reduced by the inhalation of acetyl-b-methycholine chloride (2.5 per cent) for three to four minutes there was no benefit accorded by the previous oral administration of Phenergan (25 to 50 mg.), but one normal subject obtained almost normal capacity in less than a minute when Pyribenzamine (1.5 per cent) solution was inhaled for two minutes following the choline chloride induced spasm. In normal subjects, oral Phenergan suppressed or minimized the slight subjective symptoms induced by the inhalation of histamine (3 to 10 per cent) aerosol, although the vital capacity was unchanged.

Salva and Badell[290] used Phenergan (25 mg. daily) in the treatment of radiation sickness. On five patients who took the drug during a second period of irradiation, there were no symptoms of intolerance. An additional twelve patients, who during the first course of a period of irradiation had shown symptoms of radiation sickness were also treated. In each instance, the patient was able to complete the full course without any symptoms of intolerance. In one patient, in whom there was marked edema of the cheeks and eyelids and dermatitis of the malar region, the administration of Phenergan (25 mg. daily) caused the lesions to dry and the edema to diminish within twenty-four hours, a complete cure occurring in five days. The causal relationship in this case might well be questioned since there was no possibility of control studies being done and no way of knowing how long the edema would have lasted without treatment.

An indication of how Phenergan may act on the nervous system is reported by Sigwald.[291] The intravenous injection of Phenergan abolished the spasm and clonus and normalized the tendon reflexes of four patients with pyramidal syndromes, but failed to influence the paralysis and the Babinski and automatic medullary reflexes. Of interest also is the report by Warin,[292] who discovered on observing twenty patients for six to nine months that the tolerance to Phenergan did not develop as judged by the histamine-wheal test. By prescribing the drug in one dose at night, urticaria was completely controlled, with no side effects being observed on the following day.

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(To be continued in the July-August issue.)

IDIOBLAPTIC TOBACCO SENSITIVITY

(Continued from Page 395)

order to discover food or other inhalant allergens which may then become manifest by a rise in the pulse rate.

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News Items

CHICAGO SOCIETY OF ALLERGY

The new officers for the Chicago Society of Allergy elected May 15 are: President, Townsend B. Friedman, M.D.; President-elect, Theron G. Randolph, M.D.; Secretary-treasurer, Milton M. Mosko, M.D.

CALIFORNIA SOCIETY OF ALLERGY

At the annual meeting of the California Society of Allergy, held in San Diego, May 1, 1950, the following officers were elected for 1950: President, Frank G. Crandall, Jr., M.D.; President-elect, Samuel H. Hurwitz, M.D.; Secretary-treasurer, M. Coleman Harris, M.D.

LOUISIANA ALLERGY SOCIETY

At a meeting of the Louisiana Allergy Society at the Heidelberg Hotel in Baton Rouge, April 26, new officers were elected. A roundtable discussion on bronchial asthma was held, with Dr. B. G. Efron as moderator. The panel discussion on "The Present Status of Antihistaminic Drugs" was led by Dr. Vincent J. Derbes. The newly elected officers are: President, H. Whitney Boggs, M.D.; Vice President, Vincent J. Derbes, M.D.; and Secretary, B. G. Efron, M.D.

BRAZILIAN SOCIETY OF ALLERGY

At the meeting of the General Assembly of the Brazilian Society of Allergy on December 29, the new directorate was elected. The new Board of Directors for 1950 is as follows: President, Dr. Nelson Passarelli (re-elected); Vice President, Dr. Eleuterio Brum Negreiros (re-elected); First Secretary, Dr. Haroldo Cardoso de Castro; Second Secretary, Dr. Newton Guimares; Treasurer, Dr. A. N. Sayao Lobato (re-elected); Librarian, Dr. Mario Miranda. Members of the Fiscal Council are Drs. Paulo Dias da Costa, A de Lima, and U. Fabina Alves, Ernesto Mendes, and J. B. Greco.

MEDICAL ILLUSTRATORS' DIRECTORY AVAILABLE

The Directory issue of *Graphics*, the official publication of the Association of Medical Illustrators, contains the name, address, training, professional experience, and reference to major published work of each member. Other information pertaining to the profession is included.

The journal, which was issued on June 1, is available to those requiring medical illustration service, and will be sent free of charge upon request to the Editor, Miss Helen Lorraine, 5212 Sylvan Road, Richmond 25, Virginia.

NEW YORK ALLERGY SOCIETY

The New York Allergy Society, New York Academy of Medicine, held its meeting on April 12. Six papers were read: Foreign Body Simulating Asthma, by Dr. Nathan Ravin; Pollen Studies at Ambrose Lightship, by Drs. Richard Wiseman and Israel Glazer; A New Approach to Mold Surveys, by Dr. Nathan Schaffer; Pollenosis with Negative Cutaneous Tests, by Dr. Murray Peshkin; New Antibiotics in the Treatment of Vasomotor Rhinitis, by Dr. Artell Johnson; and The Importance of Foods in Allergic Patients, by Drs. Harry Leibowitz, Alexander Chester, and Harry Markow.

BRAZILIAN SOCIETY FOR THE HISTORY OF MEDICINE

The Brazilian Society for the History of Medicine held its opening session April 19 in the Noble Auditorium of the General Polyclinic in Rio de Janeiro with the following program: Reception of the Corresponding Member, Dr. Erich Gruen, with the address of greeting by the official speaker, Dr. Jayme de Mendonca Castro; "Medical Historical Profiles" by Dr. Erich Gruen; and "Activities of the Institute in the History of Medicine of the City of Pernambuco" by Prof. E. M. Salles Cunha. Plans were made for Brazilian representatives at the Sixth International Convention of the History of the Sciences and the Twelfth International Convention of the History of Medicine, August 14-20, 1950, in Amsterdam, Holland. Preparation was also made for the First Brazilian Convention of the History of Medicine to be held in July, 1951, in Rio de Janeiro.

FIRST INTERNATIONAL CONGRESS ON ALLERGY

Plans are maturing rapidly for the first International Congress of The International Association of Allergists at Zurich, Switzerland, September 23-29, 1951. The two national allergy societies in the United States who are official members of the I.A.A. are The American College of Allergists and The American Society of Ophthalmologic and Otolaryngologic Allergy. With sixteen of the twenty-four known existing allergy societies in the world belonging to the I.A.A., and with individual fellowships representing nearly all countries, a very excellent attendance is anticipated. The members of the Organizational and Program Committees are:

President of the Congress: Prof. C. W. Loffler, Zurich
General Secretary of the Congress: Prof. A. Grumbach, Zurich
Executive Secretary of the Congress: Dr. F. W. Wittich, Minneapolis
Members: Dr. Paul Kallós, Helsingborg
Prof. R. Meier, Basel
Prof. A. Stoll, Basel

Membership in The International Association of Allergists consists of physicians, scientists, and other professional persons qualified in allergy or those scientists representing the basic sciences from which our knowledge of allergy originates. Application blanks for fellowship or associate fellowship may be obtained by writing to the Chairman of the Executive Committee, 424 La Salle Building, Minneapolis, Minnesota.

The official languages of the Congress are English, French, Spanish, and German. The account of the session, including the papers presented and a summary of the discussion, will be edited and published as the official proceedings of the Congress. The official publication of the I.A.A. is the *International Archives of Allergy and Applied Immunology*. The subscription price is about $7.00, U. S. money. Those wishing to subscribe can order directly from the publisher, Zurich, or from the Interscience Publishers, 215 Fourth Avenue, New York City, or from headquarters, 424 La Salle Building, Minneapolis.

The International Association of Allergists is an official member of the Council for the Co-ordination of International Congresses of Medical Sciences, which has received pledges from UNESCO "to give full support and material assistance to the Council, whose aims coincide so well with those of UNESCO and WHO."

The program, as outlined in La Presse Medicale, Paris, February 4, 1950, is as follows:

Topics for Discussion:

I. Diseases due to allergies; their nature and social significance
A. Diseases due to allergies and diseases accompanied by sensitization phenomena

B. Social importance of diseases due to allergies
C. Geographical distribution of diseases due to allergies

II. Historical study of allergic damages

III. Chemical and serological studies of allergies
A. Fundamental principles of the chemistry of antigens
B. Antigenic function of haptens
C. Location of the formation of antibodies
D. Biological significance of complete and incomplete antibodies
E. Pathogeny of allergic reactions

IV. Influence of constitution and heredity in the appearance of allergic diseases

V. Pharmacology of allergic reactions
A. Chemical constitution and physiological reactions
B. Success of the antihistaminic therapy
C. Behavior of sympathicolytic substances in allergy

VI. Diagnosis of allergic diseases
A. Standardization of the allergens
B. Interpretation of allergic reaction
C. Value of the functional examination of the lungs for the diagnosis of allergic conditions
D. Psychomatic conditions in allergic diseases

VII. Study of allergies: past and future

Outstanding scientists in Europe and the Americas will participate. The American Express Company has been appointed as the official travel agency for the Congress. The average time for the trip has been planned for two months, although shorter itineraries can be arranged to suit the individual. It is important that the chairman of the executive committee get as early as possible an approximate number of those who attend from North and South America. Plans are being made to have the majority travel to Europe and return by boat, leaving from New York City. Arrangements are also being made with Pan-American Air Lines for reservations for those traveling by plane. Because competition is so great, transportation lines will rarely issue a one-way ticket, so that it is understood that a person who travels by plane will return by plane, and those who travel by boat will return by boat. All those planning to attend are urged to register their names at 424 La Salle Building, and then they will receive a prospectus containing detailed information about the Congress.

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The many friends in the allergy world will grieve to learn of the death of Dr. J. H. Frazer, former medical director of the Arlington Chemical Company, Yonkers, New York, after a protracted illness. His many friends in the College extend their sincere sympathy to his wife, residing at 146 West 79th Street, New York 24, New York. In his numerous contacts with physicians all over the country, Doctor Frazer was instrumental in arousing interest in allergy and having them apply allergy to their practice.

BOOK REVIEWS

THE MANAGEMENT OF THE PATIENT WITH SEVERE BRONCHIAL ASTHMA. By Maurice S. Segal, M.D., Assistant Professor in Medicine, Tufts College Medical School, Boston. 158 pages, with figures. Price $3.50. Springfield, Illinois: Charles C. Thomas, Publisher, 1950.

This welcome monograph of the American Lecture Series is most timely. It is unique in that it integrates our rapidly developing concepts of the mechanism of asthma, based upon the complicated abnormal physiological responses and disturbed emotional personalities which comprise the physical and psychic components of the individual. With this broad concept the author attempts to apply proper physiological management when considering all of the activating forces and their evaluation. He stresses the importance of the immediate non-specific therapeutic measures for the patient acutely ill with asthma, and only then is the management of the underlying allergy undertaken. The therapeutic measures suggested are based principally on personal observations in the management by the author of over 500 patients with asthma. His therapy was based on extensive laboratory studies with a large variety of protecting drugs. In order to restore physiologic balance in the patient very ill with asthma, it was found necessary to use a large variety of properly balanced therapeutic measures.

There are ten chapters, with a bibliography and an index. These chapters include detailed reports on the use of protecting drugs, methods of sedation, supportive therapy, bronchiolar relaxation, bronchiolar evacuation or catharsis, therapeutic use of gases, and the management of infection and preventive measures.

In spite of the detailed physiologic and chemical studies, the book is very practical; and if its instructions are followed out, more relief to the patient severely ill with asthma will be obtained.

This book is printed on good paper stock, the figures are all clear, and the print is unusually large and readable. With its excellent binding and compact size, it is both a handy desk reference and a book to be slipped into the pocket.

METHODS IN MEDICAL RESEARCH, VOLUMES I AND II. Vol. I, V. R. Potter, Editor-in-Chief; 372 pages, with numerous figures. Price $8.00. Vol. II, J. H. Comroe, Jr., Editor-in-Chief; 361 pages, with numerous figures. Price $6.50. Chicago: Yearbook Publishers, Inc.

Review of Volume I was withheld until Volume II appeared. The governing board is composed of such outstanding scientists as Irvine H. Page, A. C. Ivy, Colin M. MacLeod, Eugene A. Stead, David L. Thomson, Henry Welch, and H. D. Green. Contributors and reviewers were selected as associate editors for their qualifications in their particular fields in medical research. Both volumes are devoted to methods and techniques. The governing board, when compiling material to make such a series useful, reasoned that there should be "appraisal and discussion of the various methods that have been proposed for the solution of some experimental problem." They realize also that it is becoming more difficult, especially in physiology, to have papers published describing techniques combined with the results obtained. In addition, these volumes provide an opportunity to publish modified techniques which frequently do not appear in print; and, lastly, they disseminate information about the various procedures developed during the war which have appeared only in official reports.

The first volume is divided into four chief self-containing sections, each representing one of the broad fields of medical research: biochemistry, physiology and pharmacology, microbiology and immunology, and biophysics including radiobiology. Step by

step methods are described, accompanied by photographs of apparatus, tables, and graphs.

The second volume is divided into three sections: Section I deals with the methods of study of bacterial viruses; Section II is on pulmonary function tests; Section III, assay of hormone secretions. Section II should be of interest to all allergists.

Both volumes are indispensable to the scientist performing laboratory techniques. These volumes with their detailed techniques are prepared more for the experienced laboratory investigator than the medical student, unless he is doing graduate work. The books are durably bound to withstand laboratory wear. Unfortunately, the volumes are of different length and width, but this is of minor importance.

CLINICA MEDICA, Lectures on Pathology and Treatment. By Nino Marsiaj, M.D. 471 pages. 39 figures. 25 pesos (Argentine money, about $4.00 American money). Mr. Bartolome Chiesino—El Ateneo, Florida 340-344, Buenos Aires, Argentina.

Introduction by Prof. Nicolas Romano. The author is a professor on the faculty of medicine, of the University of Porto Alegre (Rio Grande del Sud, Brasil). This book is a compilation of lectures on pathology and the clinical aspects of diseases commonly met in this section of South America, such as toxic allergy, Loeffler's syndromes, tropical eosinophilia, lambliasis, amibiasis, myasthenia gravis, etc. The illustrations are very clear. There is a reference bibliography following each chapter. It is to be regretted that there is no English translation of this book.

THE FUNDAMENTALS OF ELECTROCARDIOGRAPHIC INTERPRETATION. By J. Bailey Carter, M.D., F.A.C.P., Assistant Professor, Department of Medicine, University of Illinois College of Medicine; Attending Staff, Cook County Hospital, Augustana Hospital, Chicago. 406 pages. Price $6.50. Springfield: Charles C. Thomas, 1949.

This volume is intended as an introduction to electrocardiography for the general physician. It is not merely a report of research, as it presents only tested facts and the consensus of workers in the field. The material is so practical that careful study of the work will enable any physician to interpret the simpler records without difficulty. Almost all hospitals are now equipped with apparatus for electrocardiographic study.

The book recognizes the importance of serial curves in the diagnosis and management of coronary disease, especially in differentiating myocardial infarction from acute coronary failure, anginal attacks, or from acute abdominal disease and other conditions which it simulates.

Each chapter begins with an authoritative discussion, followed by a number of illustrative electrocardiograms. Some of the subjects covered are the physiological basis of electrocardiography, the technique, individual wave changes, paroxysmal tachycardia, coronary occlusion, and graphic findings in a long list of various specific diseases. At the back of the book are case histories and a glossary. An up-to-date bibliography follows each chapter.